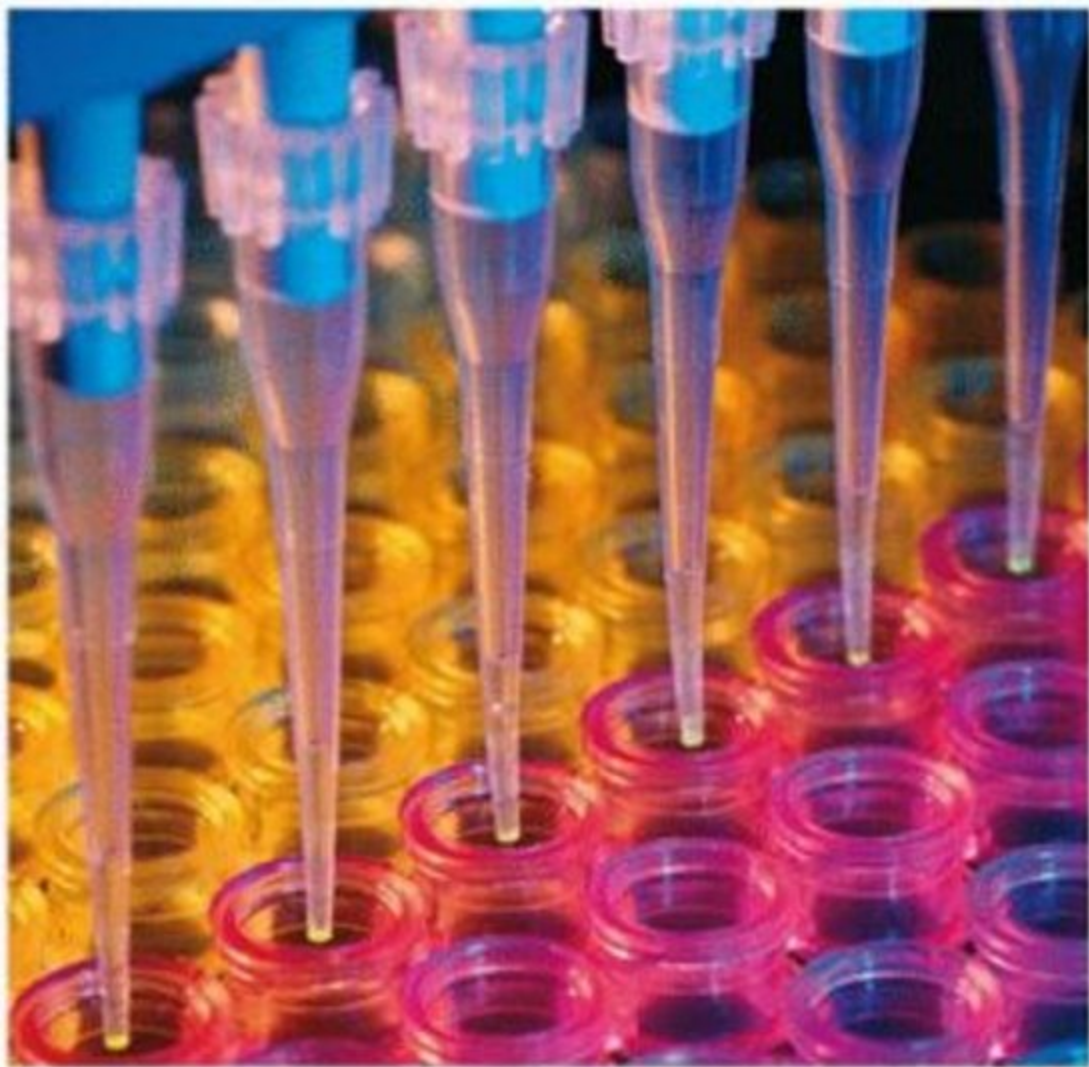


Edited by P A Carson and N Dent

# Good Clinical, Laboratory and Manufacturing Practices

Techniques for the QA Professional



RSC Publishing

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## Foreword<sup>†</sup>

The principles of good laboratory practice (GLP) are based on a simple philosophy: the basic idea is that laboratories should design, perform and report safety studies on chemicals and preparations carefully and should document all activities in such a way that studies can be reconstructed at any time afterwards. This short definition of GLP perhaps presents some danger, since individuals may interpret in different ways the word ‘carefully’ and possibly other terms in my description. Thus, the principles of GLP have been spelled out in regulations which explain in more detail the practical application of this philosophy. An important example of this application is the introduction of an internal independent-quality assurance function in laboratories: a logical but necessary interpretation of the philosophy.

One may wonder what is necessary beyond a philosophy and regulations? The several conferences and publications that have been dedicated to the subject indicate a need for further interpretation of GLP. What is the additional contribution of this book? It discusses the regulations in different countries (fortunately concluding that they are very similar) and shows how laboratories can comply with them. Being responsible for GLP compliance monitoring in The Netherlands, I consider this very useful. Much more important, however, is that the authors have successfully adhered to the spirit of GLP – its philosophy – in this book. Only on the basis of a good understanding of this philosophy is it possible to interpret GLP regulations and apply them in areas which may perhaps not have been considered in detail when the regulations were drafted, such as field trials and computer systems. Even in the more traditional GLP areas, such an understanding is a considerable help in implementing the regulations in a sensible and creative manner.

The long experience in GLP for many authors will certainly provide the reader with useful examples of solutions to ‘GLP problems’. With this valuable information and with appreciation of the spirit of GLP, the reader should be better armed to promote the quality of safety testing of chemicals and preparations – the purpose for which GLP has been introduced.

*W. H. Konemann*

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<sup>†</sup>Originally published in *Good Laboratory and Clinical Practices*, P.A. Carson and N.J. Dent (eds), Heinemann-Newnes, 1990.



# Preface

The primary aim of this book remains as for the first edition, namely to provide practical and detailed advice to the Quality Assurance (QA) professional who is responsible for monitoring compliance with legal requirements and accepted 'good practice' standards. Clearly, however, it will also be of value to those in industry, contract research organisations, universities and government establishments who are the subject of inspection and audit. These may well include study directors, facility managers, toxicologists, ecotoxicologists, technicians, analytical chemists, research clinicians, process managers and others with related administrative responsibilities.

Furthermore, the principles are becoming adopted as a means of assuring the general robustness of any data that are likely to be scrutinised by external bodies, for instance in the context of patents, marketing, courts of law, journal review committees and so on. Indeed the apparent growth of reported misconduct within the scientific community<sup>1,2</sup> led to the proposal by the deputy editor of an American journal that papers should be accepted for publication only if the authors agreed to an audit of primary data. Following an allegation of misconduct by a Nobel laureate, investigating scientists appointed by the National Institute of Health audited every piece of raw data generated during the research. The more-recent fabrication of 'groundbreaking' stem-cell research by a Korean cloning scientist further emphasises the problem.<sup>3</sup> Thus, the disciplines described also represent management techniques and good documentation practice to ensure a high-ethical standard in the conduct of any research undertaking.

The terms 'Quality Assurance' and 'good practice' are increasingly being embodied in legislation and quasi-legislation, and are adopted widely by industry. In the context of this book good laboratory practice (GLP) refers to those regulations, which were originally introduced to assure the quality and integrity of safety data generated in non-clinical laboratory studies in selected industry sectors. It addresses all those aspects of laboratory activities that can influence the results produced and their subsequent interpretation.

These include:

- Staff selection and training
- The handling of test materials.
- Choice of test method.
- Quality of measurements.
- Maintenance and calibration of equipment.
- Sample and data curation.

Later developments extended the scope of GLP from classical toxicology and pharmaceuticals to environmental studies and the generation of safety data (including toxicology, ecotoxicology and physio-chemistry) for any 'new chemical substance' (in EC terms). Any work carried out in support of GLP studies, such as characterisation and chemical analysis, also has to be performed to the

same standard as that of the main study. The number of laboratories claiming compliance has grown significantly since the first edition was published.

Many of the principles underpinning the GLP requirements are also adopted for assuring the quality of clinical research practice and for the manufacture of certain consumer products. Good clinical research practice (GCP) was originally introduced, mainly for the pharmaceuticals industry, to ensure that clinical studies were conducted in accordance with recognised scientific and ethical standards and that data of high quality were produced. Since the first edition there has been an explosion in guidelines and laws relating to GCP. Notable examples include EU Directives and the International Conference on Harmonisation. GCP has also spread geographically to the developing world and expanded scope to include animal health.

Good manufacturing practice (GMP), the oldest of the GXPs, was introduced primarily to control the quality of drugs during manufacture. Many of the principles of GCP and GMP are gradually becoming adopted by progressive companies as the standard for evaluation and manufacture in other personal product areas such as cosmetics, toiletries and dental products. Again support work for GCP and GMP studies, such as drug metabolism and analysis of clinical specimens, is increasingly being undertaken to a standard equivalent to that of the parent study.

‘Quality Assurance’ in the present context describes those management procedures used for the independent monitoring of a company’s compliance with the requirements of these good practices. Its disciplines are also transferable to auditing compliance with any quality system.

The first edition concentrated on the principles of QA and their application in relation to GLP, with only a single chapter devoted to each of GCP and GMP. The second edition addresses this imbalance.

Additional management systems with philosophy similar to that of the regulatory ‘GXPs’ have also gained widespread acceptance within industry. Examples include

- OSHAS 18001 for health and safety
- ISO14001 for environmental protection
- ISO17025 for testing and measurement laboratories or service organisations.

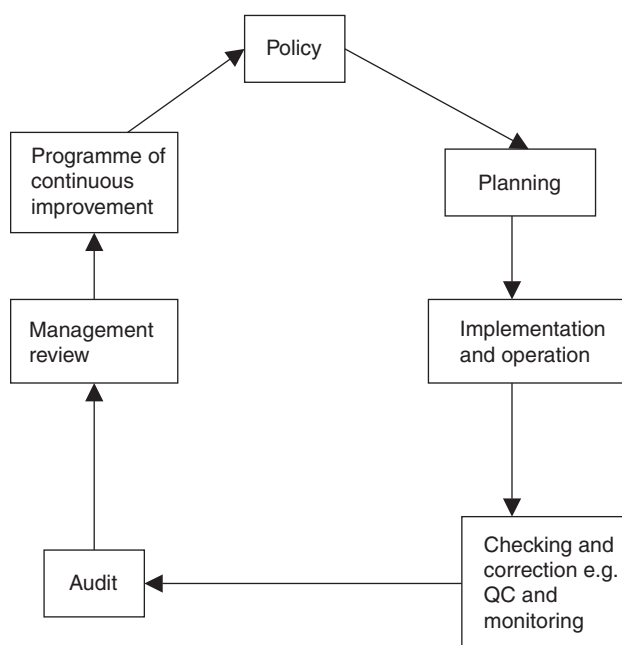
Common to all ‘good practices’ are the general underpinning elements shown in Figure 1.

Thus, this second edition, containing 40 chapters again written by a team of recognised world experts,

- expands the contents of GCP and GMP sections to a level equivalent to that devoted to GLP
- reflects developments in legislation in GCP, GLP and GMP since the first edition
- includes other quality management systems and demonstrates how a unified approach can be adopted in assuring quality of compliance with any of the systems discussed.

Space prohibits encyclopaedic description of every aspect of all the management systems. The approach, therefore, is to provide an authoritative overview of the general principles using selected examples to highlight practical implementation in greater detail.

Part 1 of the book opens with an introduction to the historical background to GCP together with its legal status and an outline of the fundamental principles underpinning the practice. Chapter 2 describes the importance of GCP protocols and associated documents such as Case Report Forms and Informed Consent procedures. It clarifies the function of QA in helping to ensure that clinical research is conducted to high standards by unearthing potential problems early in the planning stages. As with all management systems, following written operating procedures based on accepted and approved techniques is crucial to assuring compliance with the requirements of the protocol in a sustained and repeatable manner. Chapter 3 therefore discusses the use of Standard Operating Procedures (SOP) within the GCP framework. The ethical considerations of proposed clinical trials must first be reviewed and given support by independent ethics committees before studies can commence (Chapter 7). Chapter 4 addresses the detection and reporting of adverse events observed



**Figure 1** Common features of quality management systems

during a clinical trial, which is important both to protect the well-being of trial participants and in risk-benefit analysis to support subsequent studies and eventual commercialisation. Once a clinical trial is complete, it is impossible to build-in quality retrospectively. For this reason, as discussed in Chapter 5, trial performance is monitored by a series of ongoing independent site audits pre-start-up, during the ‘live phase’ and upon completion of the study. These will include audits of raw data and final study reports, the subject of Chapter 6. Such *quality audits* rely on representative samples to confirm whether or not agreed management procedures have been adhered to, and to assess overall quality and compliance with the protocol and GCP requirements. More detailed ongoing *quality control* techniques including checks on 100% samples will have been previously conducted as explained in Chapter 9. Chapter 8 illustrates how interfaces between different quality standards pose opportunities for confusion and breakdown in quality by reference to the GCP clinical research team’s work and the GMP manufacture of the investigational test products. Prior to the evaluation of drug efficacy using patients with the target disease, trials on healthy volunteers are used to assess the safety and pharmacology of the drug, and the special challenges posed in these ‘Phase 1’ studies are the focus of Chapter 10. As previously mentioned, in order to ensure any work produces quality product, in this case a final clinical report, it is essential that all phases are conducted to the same high standard. Thus, Chapter 11 covers the application of GCP to supporting laboratory investigations.

Part 2 is devoted to GLP. The historical developments, which led to the introduction of GLP and its current legal status, are expounded in Chapter 12 along with a brief outline of the underlying principles. The details of international legislation on GXPs differ from country to country. This is illustrated by the Appended table at the end of the book which compares global interpretation of the GLP rules. This provides a map with which the reader can navigate their way through the various standards. Although space prevents detailed discussion of the implications of the different GLPs, a more comprehensive version of the table is obtainable from the author. The same approach can be adopted to highlight variations between international GCPs and GMPs. The role

of QA in helping to ensure compliance with the GLP requirements is addressed in Chapter 13 and subsequently expanded by more discussion of the Master Schedule (Chapter 14), Study Plans (Chapter 15), Standard Operating Procedures (Chapter 16) and the QA Inspection Programme (Chapter 17) including Report and Data Audits (Chapter 18). Chapter 19 provides guidance to QA for contracted studies. The GLPs were initially developed to control the quality of pre-clinical, mammalian toxicology safety studies. How the scope has been extended is illustrated by their application in Pharmacology (Chapter 20), Analytical Chemistry (Chapter 21), Drug Metabolism studies (Chapter 22), Histopathology (Chapter 23), Ecotoxicology (Chapter 24) and Animal Health Trials (Chapter 25).

Part 3 is dedicated to GMP. Its origins and regulatory status is given in an introductory chapter (Chapter 26). Like other quality systems key-basic requirements involve

- clear definition and review of manufacturing processes to ensure that products are consistently made of the required quality and within specification;
- validation of critical phases of the process and any significant changes;
- staff selection and training;
- suitability of premises, services and equipment;
- correct materials, containers and labels;
- approved written procedures and instructions, suitability of storage and transport;
- record keeping and recording of data;
- product distribution and recall;
- complaints procedures;
- quality control including analysis and formal release of materials; and
- quality assurance (QA).

Sections on SOPs (Chapter 27), release of bulk and finished products (Chapter 28), and chemistry and microbiology quality control (Chapter 30) illustrate some of these in greater depth. The manufacture of certain products presents their own unique problems and as well as the general GMPs, additional requirements apply. These are exemplified by discussion of the manufacture of investigational medicinal products (Chapter 29) and for manufacture of sterile products (Chapter 31).

Part 4 of the book contains guidance for QA staff irrespective of the GXP.

Thus, Chapters 32 and 33 cover statistics and metrics, respectively, while advice on document control from concept to archiving is given in Chapter 36. It is to be appreciated that review of the documentation package (*e.g.* by a regulatory agency) should enable the reviewer to reach the same conclusions as those who compiled the package, and would permit the reconstruction of the study or of the batch of material manufactured. Once finalised and signed-off, the documentation package should be protected from loss or amendment.

Clearly, for any of the GXPs, quality can be affected by any component of the supply chain, *e.g.* raw-material suppliers, contract manufacture and analysis, contract phases of GCP or GLP studies, product distribution and storage. The interface between sponsor and contractor is particularly vulnerable, and the need to audit third parties is evidenced by Chapter 35 on audits of suppliers for animal studies (an initiative of the French Quality Assurance Society) and Chapter 34 on suppliers in the manufacturing environment; Chapter 19 is also helpful. The general principles from these chapters are more widely applicable.

Disciplines for data recording have been highlighted throughout. The special concerns relating to the recording, analysis and storage of *computerised* data and computer system validation are included in Chapter 37.

Quality work can only be produced by carefully selected and well-trained staff. This is the subject of Chapters 38 and 39, which also embrace the importance of recording individual development and training.

Regulated companies may become overloaded with quality management systems, including the GXPs, ISO standards, *etc.* The adoption of a harmonised system offers a means of overcoming the excessive staff pressure, bureaucracy and associated on-costs (Chapter 40).

Finally, a glossary of common terms used throughout the industry is provided at the end of the book, followed by a list of websites which may also prove useful in supplementing chapter references.

Phillip Carson

Nigel Dent

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# Preface<sup>†</sup>

The terms 'Quality Assurance' and 'good practice' are increasingly being embodied in legislation and quasi-legislation, and are adopted widely by industry. In the context of this book good laboratory practice (GLP) refers to those regulations, which were originally introduced to assure the quality and integrity of safety data generated in non-clinical laboratory studies in selected industry sectors. It addresses all those aspects of laboratory activities, which can influence the results produced and their subsequent interpretation. These include:

- Selection and training of staff.
- The handling of test materials.
- Choice of test method.
- Quality of measurements.
- Maintenance and calibration of equipment.
- Sample and data creation.

Later developments extended the scope of GLP from classical toxicology and pharmaceuticals to environmental studies and the generation of safety data (including toxicology, ecotoxicology and physico-chemistry) for any 'new chemical substance' (in EC terms). Any work carried out in support of GLP studies, such as characterization and chemical analysis, also has to be performed to the same standard as that of the main study.

Many of the principles underpinning the GLP requirements are also adopted for assuring the quality of clinical research practice and of the manufacture of certain consumer products. Good clinical research practice (GCRP) was originally introduced, mainly for the pharmaceutical industries, to ensure that clinical studies were conducted in accordance with recognized scientific and ethical standards and that data of high quality were produced.

Good manufacturing practice (GMP), similarly, was introduced primarily to control the quality of drugs during manufacturing. Many of the principles of GCRP and GMP are gradually becoming adopted by progressive companies as the standard in other personal product areas such as cosmetics, toiletries and dental products. Again support work for GLP, GCRP and GMP studies, such as drug metabolism and analysis of clinical specimens, is increasingly being undertaken to a standard equivalent to that of the parent study.

'Quality Assurance' in the present context describes management procedures for the independent monitoring of a company's compliance with the requirements of these good practices.

The aim of this book is to provide detailed authoritative guidance on compliance with the individual components of GLP, GCRP and GMP programs; the 27 chapters are written by a team

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<sup>†</sup>Originally published in *Good Laboratory and Clinical Practices*, P.A. Carson and N.J. Dent (eds), Heinemann-Newnes, 1990.

of recognized world experts. The background to the development of these good practices is summarized in Part I, along with clarification of individual responsibilities within an organization for compliance with GLP requirements. Since different authors have used either OECD guidelines or local legislation/codes of practice as their point of reference, Part I also includes a chapter on the international status of GLP requirements.

Part 2 of the book is devoted to the whole gamut of factors that affect data quality from study planning to study conduct and reporting; it gives advice on documentation, inspections, audits and archiving, together with the scheduling of a monitoring program. Part 3 is devoted to a discussion of the application of general quality principles to selected specialized areas, including,

- Ecotoxicology
- Drug metabolism
- Analytical chemistry
- Pathology
- Computerization
- Inspections by 'competent authorities'
- GCRP
- GMP

Guidance is also provided on Quality-Assurance units, the use of statistics in data audits, training, and on the QA implications of the sponsor/contractor interface for GLP studies performed by contract houses.

The appendices provide a comparison of the key requirements of the different main pieces of legislation and a specimen company policy statement, and the book concludes with a glossary and a bibliography to supplement those references provided with original chapters.

This book is intended primarily for Quality-Assurance auditors who have responsibility for monitoring compliance with legal requirements or accepted standards and guidelines. Clearly, however, it will also be of value to those in industry, contract research organizations, universities and government establishments who are the subject of inspection and audit. These may well include study directors, facility managers, toxicologists, ecotoxicologists, technicians, analytical chemists, research clinicians, process managers and others with related administrative responsibilities.

Furthermore the principles are becoming adopted as a means of assuring the general robustness of any data that are likely to be scrutinized by external bodies, for instance in the context of patents, marketing, courts of law, journal review committees and so on. Indeed the apparent growth of reported misconduct within the scientific community' led to the proposal by the deputy editor of one American journal that papers should be accepted for publication only if the authors agreed to an audit of primary data. Following a recent allegation of misconduct by a Nobel laureate, investigating scientists appointed by the National Institute of Health audited every piece of raw data generated during the research. Thus the disciplines described also represent management techniques and good documentation practice to ensure a high ethical standard in the conduct of any research undertaking.

*Phillip Carson, Nigel Dent*

- (i) M. Kane, *Chemistry in Britain*, 1989, (June), 557.
- (ii) H. Gavaghan, *New Scientist*, 1989 (May), 26.



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## **Part 1: Good Clinical Practice**





## CHAPTER 1

# Introduction: Good Clinical Practice

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## 1.1 INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki,<sup>1</sup> and that the clinical trial data are credible. Although born as a guideline, in many parts of the world it is now a legal requirement to work to GCP standards when conducting clinical research. The large body of literature on the subject of GCP confirms its importance and the seriousness with which those working in clinical research regard the subject. At its most basic level, GCP is a set of rules establishing the standards for performing and documenting clinical trials so that participating subjects are protected and that cross-national acceptance of study data by clinicians and regulators is achieved.

## 1.2 BACKGROUND

Following the well publicised medical research horrors that were described at the Nuremburg trials, during which it was revealed that Nazi physicians had undertaken experiments on prisoners without their consent and without regard for the individual's well-being, the Nuremburg Code was published in 1949 (US Government Printing Office). The Nuremburg Code described for the first time the principles of Informed Consent. This became the basis for the Declaration of Helsinki made by the World Medical Association (WMA) at their annual meeting in Helsinki in 1964 (see Chapter 7, Research Ethics Committees). Just before this, in 1962, the Drug Amendment Act had been approved in the United States. This became the Food and Drug Administration (FDA) Regulations governing clinical research which obligated investigators to inform the FDA of any proposed clinical trials, required the submission of pre-clinical data to support the proposed trials, and required informed consent of the trial subjects to be obtained and that the trial results would be reported. The FDA Regulations of 1962 were subsequently expanded to include Good Manufacturing Practice (GMP) in 1963, Institutional Review Boards in 1971 and GCP in 1977. This was the start of a framework of legislation and guidelines that are now in place covering the majority of clinical research in almost every country in the world.

During the 1970s and 1980s other countries developed their own guidelines for GCP. In Europe, guidelines were developed in a number of countries including Austria, Finland, France, Germany,

Greece, Ireland and the United Kingdom. The Nordic GCP guidelines were also developed. Eventually, in 1990, there was some harmonisation of GCP standards to be followed across Europe when the European Committee for Proprietary Medicinal Products (CPMP) GCP guidelines were issued. In other regions of the world, Canada, Israel and Japan also developed GCP guidelines and the World Health Organisation (WHO) issued their set of GCP guidelines in 1993, by which time it was becoming increasingly obvious that a global standard for GCP was required. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recognised this need in 1991 and set up an Expert Working Group to draft a guideline on GCP. This was issued as a finalised guideline, ICH E6 GCP Consolidated Guideline,<sup>2</sup> in May 1996, and was adopted by the three main ICH regions – CPMP in Europe, published in the Federal Register in the United States and adopted by the Ministry of Health and Welfare (MHW) in Japan, in the following year. This GCP guideline also attracted considerable interest from those countries and organisations outside the three main ICH regions such as Canada, South Africa, Australia and the WHO. Thus the ICH GCP guideline quickly became the most widely accepted and followed GCP guideline globally. The benefits of a global standard for drug development can be huge, both as a cost saving by not having to repeat similar studies in different countries, and by allowing the introduction of new treatments more quickly.

### 1.3 SCOPE OF GOOD CLINICAL PRACTICE

Much of the drive for one standard of GCP is the multi-national nature of clinical research and the consequent need to have common standards of ethics, behaviour and process so that the data are equally acceptable to regulatory authorities worldwide. The ICH GCP guideline should be followed when gathering clinical trial data that are intended to be submitted to regulatory authorities, and the principles can be applied to all clinical investigations that may impact on the safety and well-being of human subjects. There has been some resistance from the academic community to fully comply with GCP when performing medical research not intended for a licence submission. However, it does not seem justifiable that research participants should have any lower standards of protection when involved in academic research.

### 1.4 LEGISLATION

The finalised ICH E6 guideline on GCP, which was published in May 1996 was adopted by the three main ICH regions – Europe, the United States and Japan – in the following year.

The legislation that underpins the standards of GCP that must be followed in clinical investigations in the three ICH regions are: the US FDA Code of Federal Regulations Title 21(21 CFR), the European Union (EU) Directives and the Japanese Pharmaceutical Affairs Law. The EU Directives cover all phases of clinical research, including post-marketing (Phase IV therapeutic use) studies, but the FDA and Japanese regulations only cover those investigations that are intended to be submitted for regulatory approval.

In the United States, the regulations in 21 CFR support applications for research or marketing permits for products regulated by the FDA. 21 CFR is kept up-to-date by the individual issues of the Federal Register; so these two publications must be read together to ascertain the latest version of any given rule. The ICH E6 GCP guideline was published in the Federal Register on 9th May 1997 (62 FR 25692) and is applicable to drug and biological products, but it remains a guidance and has not been incorporated into 21 CFR. The Guidance for Industry<sup>3</sup> published by FDA, however, notes that ‘this guidance (ICH E6) represents the Agency’s current thinking on good clinical practices’ which gives a strong recommendation that ICH E6 should be followed when performing clinical studies that are destined for submission to the FDA. The parts of 21 CFR that cover different aspects of GCP are: part 50 – Protection of Human Subjects, part 54 – Financial

Disclosure by Clinical Investigators, part 56 – Institutional Review Boards, part 312 – Investigational New Drug (IND) Application and part 314 – Application for FDA approval to market a new drug.<sup>4</sup>

Within the EU, legislation to implement GCP is driven by two directives. Directive 2001/20/EC<sup>5</sup> took effect on 1st May 2001 and required member states to implement GCP in the conduct of clinical trials on medicinal products for human use as from 1st May 2004. This was accompanied by five legally binding guidance documents<sup>6</sup> giving more details on applications to competent authorities, ethics committees, obtaining a EudraCT number and two guidances that describe the reporting of adverse reactions. By the end of 2005 most of the 25 member states had legislation in place to achieve this. To support this, another EU Directive 2005/28/EC<sup>7</sup> has been introduced which lays down the principles and detailed guidelines for GCP as regard to investigational medicinal products (IMPs) for human use as well as the requirements for authorisation of the manufacturing or importation of such products (see Chapters 8 by Bailes and 27 by Edy). Directive 2005/28/EC took effect on 20th April 2005 and member states were directed to incorporate it into local law by 29th January 2006. This directive lays down the principles of GCP, the requirements for authorisation of the manufacture or importation of IMPs and the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures. It is interesting to note that the directive requires the 1996 version of the Declaration of Helsinki and the ICH GCP guidelines that reached a consensus in 1995 to be followed. The trial master file will provide the basis for audit and inspection and will consist of essential documents the contents of which will be published in an additional guidance.

In Japan, ICH GCP was published as 'Japanese Technical Requirements for New Drug Registration 1997'<sup>8</sup> by the MHW and has been enforced as Ministerial Ordinance Number 28 since April 1997. The Pharmaceutical Affairs Law and subordinate regulations were amended using ICH GCP as a guideline and implemented in April 1998.

## 1.5 RESPONSIBILITIES

The ICH GCP guideline is divided into eight chapters beginning with a glossary in Chapter 1, which aims to ensure a common understanding of terms. Chapter 2 states the underpinning Principles of ICH GCP which have their origin in the Declaration of Helsinki. The responsibilities of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), Investigator and Sponsor are clearly set out in Chapters 3, 4 and 5, respectively. The guidance to ensure the documentation that complies with GCP is given for the Clinical Trial Protocol, the Investigator's Brochure and the Essential Documents for the Conduct of a Clinical Trial are present in Chapters 6, 7 and 8, respectively.

### 1.5.1 Responsibilities of the Institutional Review Boards/Independent Ethics Committees

Under GCP the ethics committee is responsible for safeguarding the rights, safety and well-being of all trial subjects. This usually involves the ethics committee reviewing the research proposal and the sites at which it is proposed to conduct the research. To review the study it is suggested that a comprehensive list of documents are reviewed; the protocol and investigator's brochure are obvious candidates, but the list also includes subject recruitment procedures, including any advertisements, written patient information and the informed consent signature form. Any compensation payable to the subjects has to be declared, and the committee can review any additional document it feels necessary to fulfil its responsibilities. The committee should give its decision within a reasonable time, and review any amendments to the approved protocol before they are implemented. To review the research site it is suggested the curriculum vitae (CV) of the investigator is considered together with any other relevant documentation.

It is required that the IRB/IEC conducts ongoing review of the research, for example at yearly intervals, and it may request additional written information for the trial subjects if appropriate to protect their rights, safety or well-being. If a trial is proposed, which may include adults unable to consent for themselves, consent should be sought from a legally acceptable representative. The implementation of the EU Directive on clinical trials since May 2004 has helped to harmonise this requirement within the EU and an acceptable way forward has been found to conduct research in those unable to consent for themselves in most EU member states. GCP allows for research in the emergency situation where consent may not be possible, and if such research is to continue, the role of the ethics committee is pivotal in ensuring that an acceptable form of 'consent' is included. Under GCP subjects may receive payment, particularly when they are not expected to derive any benefit from the treatment under investigation, such as in phase I (human pharmacology) studies (see Chapter 10 by Cope), however, payments must be prorated and approved by the IRB/IEC beforehand.

## **1.5.2 Responsibilities of the Investigator**

Investigators are obviously crucial members of the team responsible for the satisfactory completion of a clinical trial and their responsibilities under GCP are therefore described in some detail in the guideline.

*1.5.2.1 Investigator Qualifications and Agreements.* The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical trial, and provide documentary evidence of this to ethics and regulatory bodies. He/she should be thoroughly familiar with information on the investigational product (IP) provided by the sponsor; permit monitoring, audit and inspection of his/her conduct of the trial and, of course, comply with GCP. If any duties or responsibilities are delegated, a list of delegated duties and responsible persons should be kept.

*1.5.2.2 Adequate Resources.* The investigator should be able to demonstrate adequate potential subjects for the study as well as time, equipment, qualified staff and adequate facilities to conduct the trial properly and safely.

*1.5.2.3 Medical Care of Trial Subjects.* Under GCP a qualified physician (or dentist when appropriate) should be responsible for trial-related medical decisions. It is recommended that a subject's primary physician be informed of a subject's participation in a clinical trial, if the subject agrees. If a subject withdraws prematurely, an investigator should make reasonable attempts to determine 'why', in case it is due to an adverse event, although it must be remembered that a subject can withdraw at any time without giving a reason.

*1.5.2.4 Communication with IRB/IEC.* Before initiating the trial an investigator should either have written and dated approval/favourable opinion for the trial protocol and associated documents submitted for review. Any updated documents should be submitted by the investigator for review and approval before implementation, except to remove a potential hazard to the subject (see Chapter 7 by Eckstein).

*1.5.2.5 Compliance with the Protocol.* GCP requires that the investigator complies with the approved current version of the protocol, and that any deviations are documented.

*1.5.2.6 Investigational Products.* Responsibility for IPs accountability rests with the investigator. In practice it is often delegated to a pharmacist to store IPs and maintain records of delivery

to the site, dispensing and return of products used by subjects in a clinical trial and disposal or return of the IP to a sponsor.

*1.5.2.7 Informed Consent of Trial Subjects.* One of the fundamental ethical principles of the Declaration of Helsinki is the investigator's responsibility to ensure that subjects are informed, both orally and in writing, and that this consent is documented in accordance with applicable regulatory requirements and approved by an IRB/IEC. Subjects should not be coerced or unduly influenced to participate or continue their participation, and none of the information may waive any legal or other rights of the subject or liability of the investigator and institution from negligence. Written information and the informed consent form must be updated and approved by the IRB/IEC if new information relevant to a subject's safety becomes available during the course of a trial. If the subject is unable to provide informed consent the subject's legally acceptable representative should be informed in a similar manner. The language used both orally and in writing, to present information, should be as non-technical as possible, and the subject (or legal representative) should be given ample time to ask questions before reaching a decision regarding participation. Before participation the written informed consent form should be signed and personally dated by the subject or subject's legally acceptable representative, and by the person who conducted the informed consent discussion. If a subject (or legal representative) is unable to read, an impartial witness should be present and sign the consent form to confirm that appropriate oral information was given.

GCP also defines what should be included in the oral and written information. It should be stated that the trial is research, its purpose explained, the number of subjects to be included and its duration. Details of treatments are to be given and any procedures, possible risks and benefits, alternative treatments, compensation in the event of trial-related injury, expenses or payments are to be explained. It must be made clear that participation is voluntary, that the subject's medical records may be examined by third parties, and that every effort will be made to preserve their confidentiality. Also, that they will be informed if new information becomes available, whom to contact for further information and the circumstances under which the trial may be terminated. The subject or his representative should receive a copy of the signed informed consent form. There is further guidance on special situations such as non-therapeutic research in subjects unable to consent, or research in emergency medicine. Thus, GCP requires that a lot of information is given to subjects, and the challenge facing researchers is how to convey this information in a succinct, accurate and understandable way.

*1.5.2.8 Records and Reports.* The investigator is responsible for the accuracy, completeness, timeliness and legibility of the data reported to sponsors. Reported data that are derived from source documents, such as patient's medical records, should be consistent with those documents and any change or correction to a Case Report Form (CRF) should be dated, initialled and explained. Inspectors will check data in sponsor's electronic files with source documents and an audit trail, both paper and electronic, needs to exist to track any corrections or changes. At the end of the GCP guideline there is a list of essential documents which a sponsor and an investigator need to create and keep during the course of a clinical trial, and at least for 2 years after the last marketing authorisation of the IP. It is very difficult for the sponsor to know when the last marketing authorisation has been granted and in practice they may wish to keep the evidence until, for example, 5 years after withdrawal of the product from sale.

Financial arrangements between investigators, institutions and sponsors should be documented, and on the request of competent authorities the investigator should make available all trial related records for direct access. Investigators are responsible for submitting progress reports to the IRB/IEC, usually annually, and serious adverse events (SAEs) occurring in their trial subjects to the sponsor immediately. Investigators may also have a responsibility to report SAEs occurring with



the IP to regulatory authorities and ethics committees. When the final report of a trial is available or if a trial is terminated prematurely an investigator may also have reporting responsibilities to subjects, ethics committees and regulatory authorities.

### 1.5.3 Responsibilities of the Sponsor

The largest section of the ICH GCP guideline concerns the responsibilities of sponsors and this chapter can only give a flavour of the extent of those responsibilities. In the guideline 23 aspects are covered ranging from quality assurance and quality control to multi-centre trials. Summarising, the main responsibilities are as follows:

Sponsors should have systems in place to maintain quality assurance and quality control with written standard operating procedures (SOPs). A sponsor may transfer any or all of these duties to a contract research organisation (CRO), but the ultimate responsibility for quality and integrity remains with the sponsor. The sponsor should designate appropriately qualified medical personnel to be available to advise on medically related trial questions or problems. The sponsor should utilise qualified individuals (*e.g.* biostatisticians, pharmacologists, *etc.*) throughout all stages of the trial process from protocol and CRF design to database preparation and analysis and report writing. The GCP guideline makes reference here to other relevant ICH guidelines such as those concerning selection of a comparator (E8), statistical issues (E9) and contents of a clinical study report (E3). It also refers to setting up independent data monitoring committees to assess safety and critical efficacy endpoints.

Most trial data are now handled and stored electronically by sponsors and the guideline includes the precautions a sponsor should take to ensure completeness and accuracy of electronic data. There is reference to the last section of the guideline listing essential documents for the conduct of a clinical trial and it reminds the sponsor to retain those documents to comply with local regulatory requirements, even for a period of time after discontinuation of the product.

Sponsors are responsible for selection of investigators, should supply them with a protocol and investigator's brochure, and document, in an agreement, their willingness to conduct the trial according to GCP, the protocol, to permit monitoring, auditing and inspection and to retain trial related essential documents. Sponsors are also responsible for providing indemnity for subjects and investigators against claims arising from the trial, except those for malpractice or negligence by the investigator. Sponsors usually assist in the preparation of notifications or submissions to regulatory authorities, and obtain adequate confirmation, of review of all relevant documents by an ethics committee, from the investigator.

Information on the IP should be adequate to support the proposed trial, and it is the sponsor's responsibility to justify the study programme by preparing and updating an investigator's brochure. Sponsors should ensure the IP is characterised, manufactured and packaged to GMP, and provide information on labelling, storage, handling and method of unblinding in a blinded study. Sponsors are responsible for supplying investigators with IP, when ethics approval has been obtained, and keeping details of all shipments, returns and disposals of the IP. The sponsor is responsible for ongoing safety evaluation of the IP and for timely notifications to investigators and regulatory authorities of adverse drug reactions, including expedited reporting of those that are serious and unexpected.

Another important function of sponsors is to provide monitors (see Chapter 9 by Bevan and Ollier) to verify that the conduct of the trial is in accordance with GCP, applicable regulatory requirements and with the protocol, that the rights of subjects are protected and that the reported data are complete, accurate and verifiable from source documents. Qualified monitors should be selected by the sponsor and trained in all aspects of the trial. The amount of monitoring should be decided by the sponsor and will depend on the design and complexity of the trial, but in general will involve regular on-site monitoring visits before, during and after the trial. Monitoring activities

should be documented. Monitor's responsibilities are described in the GCP guideline and are basically to check that the investigator fulfils all aspects of his responsibilities according to GCP from protocol compliance to performing source data verification to check correct recording of data concerning the trial subjects in the CRF, or transferred electronically to the sponsor.

Having run the study to GCP most sponsors conduct their own routine audit of the study documentation (see Chapter 6 by Birnie) by their own or external auditors, to see how well standards have been achieved and to identify possible training needs. Auditors should be independent of the trial system and properly trained to perform audits. Sponsors should have SOPs describing what, when and how audits will be performed and reported. Findings should be documented, but not routinely submitted to regulatory authorities, who may perform their own inspections, and if serious non-compliance is found, request copies of sponsor's audit reports. If monitoring, auditing or inspection reveals non-compliance by the investigator, institution or sponsor's staff, the sponsor is responsible for taking prompt action to secure compliance. If non-compliance is serious and persistent and a sponsor closes down an investigator's site, the regulatory authority must also be informed. If a trial is terminated prematurely, the investigators, regulatory authorities and ethics committees must all be informed, and the reason explained.

## 1.6 FRAUD AND MALPRACTICE

The first inspections of clinical studies to ascertain the standards of conduct and record keeping were performed in the United States by the FDA in the early 1960s. In 1977 the Clinical Inspection Program was incorporated into the FDA's Bioresearch Monitoring Program, which was set up to ensure the guidelines and that regulations were being followed. During the early years of this Bioresearch Monitoring Program a significant number of malpractices were discovered, which led to a number of legal prosecutions. Over the years the number of FDA inspections has increased significantly and now around 400 routine inspections are conducted by FDA every year covering sites in the United States and worldwide. This has led to a significant fall in the amount of misconduct detected. The most frequently encountered malpractices found by FDA inspectors at investigator sites were failure to follow the protocol and failure to maintain adequate and accurate case histories both of which should have been picked up with adequate monitoring.

In Europe some countries have had active inspection programmes, often voluntary, since the late 1990s. In 2001, Directive 2001/20/EC introduced the requirement for member states to appoint inspectors and to perform compulsory GCP and GMP inspections of all sites concerned with a clinical trial. The recent Directive 2005/28/EC has added more detail on the educational and training requirements for inspectors and inspection procedures. Guidance documents will be developed which will outline the common provisions on the conduct of inspections and inspections will be conducted in accordance with the guidance to support mutual recognition of the inspection findings. Harmonisation of inspection guidance will be achieved through joint inspections, agreed processes and procedures and sharing of experience and training.

Japan also has an inspection programme which reviews compliance with GCP at investigator sites. Inspections are conducted by the Compliance Review Department in the Organisation for Safety and Research (KIKO). The number of inspections has increased gradually from 14 in 1997–1998 to 112 in the year 2000–2001.

Potential fraud is taken very seriously by all concerned, especially sponsors. In practice, potential fraud at an investigational site is usually picked up initially by the sponsor during the routine monitoring and/or audit activities that are required by GCP. However sometimes the GCP guidelines require interpretation, as it is difficult to draft guidelines that apply to every clinical trial situation. The increasing number of inspections and subsequent training should help to clarify



the interpretation of GCP and standardise clinical research practice and also serve as a warning that fraud is likely to be detected.

## 1.7 CONCLUSION

Harmonisation of GCP through the ICH process has reduced the need for many national organisations to have their own version of GCP in countries within ICH – US, EU and Japan. For countries outside ICH some organisations have taken ICH GCP as a starting point and together with the Declaration of Helsinki have developed their own code and incorporated it into their legislation. We are still in a situation where the framework for GCP in many countries has been developed in a very individualistic way.

While GCP is very much to do with process rather than the discovery of new science, it is a dynamic subject that is evolving and being refined constantly. New developments that are likely to be noticeable over the coming years are the wider use of electronic methods for gathering the data with investigators and subjects entering the data straight into the sponsor's database. This will be accompanied by electronic storage, processing, reporting and assembling of submissions to competent authorities for marketing authorisations, all within GCP.

There can be no doubt in anyone's mind that GCP is here to stay. Academic departments have also recognised the value of conducting their research within the structured environment offered by GCP. Through legislation, education and training of all involved the standards of research involving human subjects should improve and we should all have confidence in the evidence gained from well run clinical investigations leading to improved healthcare.

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## CHAPTER 2

# **The Protocol, Case Report Form and Initial Documentation: Quality Assurance Involvement and Common Problems**

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### **2.1 PREPARATIONS FOR A CLINICAL TRIAL IN THE INITIAL STAGES: THE ROLE OF QUALITY ASSURANCE**

The use of quality assurance (QA) in the clinical trial is often a requirement, but can be viewed by all staff as potentially invasive and hazardous. Often clinical management fails to appreciate the role of QA, both in the planning, the cost and the start up of clinical trials. Their attitude has, in the past, been not wanting to involve “a necessary evil” until the study is well under way. However, this approach does appear very short sighted in hindsight, as many mistakes that occur during the clinical trial may be avoided by input from the QA department. From clinical management’s point of view, the QA department plays often a major role in preventing corrective actions being taken at a stage too late in the clinical trial, when too many patients have been recruited across several sites, and therefore an earlier audit would have prevented these at the sight concerned and lessons were learnt for other sites through monitors, bringing this information to the site itself.

Throughout this chapter, it may be noted that the author is suggesting too many roles for the QA auditor. Clinical research, however, requires that auditing by the QA department is carried out, but we should be well aware that badly planned and executed clinical trials could see the clinical trial subject suffer unnecessarily, the safety and welfare of the patient or volunteer compromised and this would naturally then reflect directly or indirectly in a very serious manner on all involved parties within the clinical trial itself.

An experienced QA auditor with several years experience in the clinical trial environment has been exposed to the deficiencies and poor preparation of many trial centres. There is, therefore, an opportunity for them to prevent the worst mistakes being made, to contribute to the success of the clinical trial and by their frequent involvement in such studies, ensure that both the protocol, the case report form and informed consent and information sheets that are key initial documentation, not only link together, but are truly reflective of the way the clinical trial should be conducted.

QA should also be part of any training plan for clinical trial staff within the sponsor office, the investigator site and particularly at the investigator meeting, where the role of audit can be clearly described and in this day and age, preparation of the site and particularly the investigator and sub-investigators for the inevitable regulatory inspection can be covered and dealt with in a systematic way.

Members of the QA department will also be aware of the size and nature of the specific clinical trial and will put together their audit plans. This, therefore, is very important in the construction of the protocol and the review of the protocol by the QA department, as they can then see not only the practicalities of their audit situation, but will give an overview on the logistics and practicalities of monitoring the study and the numbers of monitors that would be required from either the sponsor organisation or from the contract research organisation (CRO) itself.

### 2.1.1 Quality Assurance and their Involvement in the Preparation of the Protocol

The protocol is the most critical document and, regrettably, the most poorly used document at the clinical trial site. Documents supplied to the clinical trial site and the principal investigator, a great many documents descend on those persons desks prior to patient recruitment or even study staff, include the protocol, the case report forms, monitoring guidelines, ethics committee and regulatory approval, good clinical practice documentation, declaration of Helsinki, investigator's drug brochure, financial and confidentiality contracts, the laboratory manual, additional manuals for magnetic resonance imaging (MRI) or associated studies, procedures for conducting electro cardiogram (ECG) and other vital sign measurements, *etc.* When questioning most investigators as to the document they use most, the reader, I am sure will be surprised to find out that this is the case report book, and not the protocol.

Why is this – it is the author's opinion that the protocols are too complex, the subject of too many amendments and are not written in a user-friendly way, whereas the case report book, when opened, clearly tells the investigator, sub-investigator and study trial team exactly what to do on that day. To obtain this information from the protocol, often involves searching through many pages.

The author shares his experience he had with a protocol from one American company. It consisted of a 140-page protocol superseded within 2 weeks of its issue by 190-page protocol amendment. The protocol itself was completely re-produced; but where additional information was required, the information was placed beneath each line in bold type, and was the most complex document ever seen. Again, these sorts of amendments would now not be acceptable under new EU directive rules, but even so, the number and type of amendments to protocols often clearly show lack of thought and study design.

To try to overcome this, the QA department should have some input into the preparation of the final draft protocol. As auditors, QA will often see what happens when investigators try to follow poorly prepared protocols.

The protocol itself will be written by a clinical expert in the field of the medical condition involved in the study, may be by input from the clinical trial staff and from a CRO if one is involved.

The draft protocol should have additional inputs for medical reviewers, senior clinical research staff, data management, and, most importantly, statistical advice. This is then supplemented by a QA review to try to put into practice using the protocol in the audit situation.

The review should be just that – this is not a scientific or medical review in any way, and is merely to ensure that the principles of good clinical practice, the EU or other international regulations and directives where applicable are followed. The document also itself draws attention to the local laws and regulations of the countries in which the clinical trial will be conducted and most importantly that relevant approaches to Ministry of Health, hospital management, *etc.*, are covered in the protocol to allow notification and approval.

Where applicable, QA should also review the protocol for compliance with sponsor, CRO or additional standard operating procedures.

**It is once again very important to clearly state that the quality assurance input to any protocol review is not for medical purposes, to assess the principle and sub investigators or the clinical trial site**

**for their expertise (although this would be seen from earlier reviewing their CVs) but merely to see that the protocol is a document that can be understood, followed and from the point of view of quality assurance, audited at the site.**

The review of the protocol from the point of view of QA is to ensure that Section 6 of ICH GCP,<sup>1</sup> and the basic contents are available and a checklist (see Appendix A) will help the reader to establish these points. The main contents of a protocol are given in Table 1.

It is of paramount importance to remember that QA does not become involved in writing the document, or making comments on the science or the medical design.

However, any omissions from those headings suggested by ICH or local guidelines and regulations must be pointed out as part of an audit finding.

As an example a typical SOP for protocol writing and review is included as Appendix B.

**Table 1** *Contents of typical phase I clinical research protocols*

- 
- Title page
  - Protocol synopsis
  - Table of contents
  - List of abbreviations/definitions
  - Introduction (including background and rationale)
  - Study objectives
  - Study plan and procedures
    - Overall study design
    - Rationale and risk/benefit assessment
    - Rationale for study design, doses and control groups
    - Selection of study population
    - Inclusion/exclusion criteria
    - Discontinuation criteria
    - Treatments
    - IMP's identification/labelling/storage/accountability
    - Treatment regimes
    - Method of assigning subjects to treatment groups
    - Blinding/unblinding
    - Concomitant medication
    - Treatment compliance
  - Management of study variables
    - Medical examination and demographic measurements
    - Enrolment examination
    - Post study medical examination
    - Pharmacokinetic measurements
    - Determination of drug concentration in biological source
    - Pharma co-dynamic measurements
    - Safety measurements
    - Laboratory safety measurements
    - Measurement of study variables
    - Adverse events
- 

*(Continued)*

**Table 1** (Continued)

- 
- Study management
    - Monitoring
    - Data verification
    - Audits and inspections
    - Staff training
    - Changes to protocol
    - Study agreements
    - Study timetable
    - Data management
    - CRFs
    - Electronic data capture
    - Lab data
    - Pharmacokinetic data
  - Pharmacokinetic, pharma co-dynamic safety and established methodology
  - Ethics
  - Informed consent
  - Subject data protection
  - Procedures in case of emergency, overdose, *etc.*
  - List of tables/figures
- 

## 2.2 COMMON FINDINGS IN CONDUCTING PROTOCOL AUDITS SEEN BY QA

The following are some areas that the author considers should be reviewed by the QA group to fulfil their role and responsibility in ensuring the quality protocol is produced.

- (i) **Contents pages** and pagination should be checked, either in total or on a randomised basis, to ensure that these activities have been adequately addressed and the reader can use these tools to find their way through the protocol.
- (ii) **Signature pages** should contain individual signatures from key persons. The signature page should also be checked to ensure that the key people, such as the sponsor, the principal investigator, the statistician and other responsible persons such as monitors, are present with appropriate contact details. A convention should be adopted in ensuring that the month is always written, rather than numeric representation, as multi-site and multi-national studies can cause concerns with different date formats.
- (iii) **The protocol** itself should be well written, concise but detailed and in an easy to read manner.

The auditor should resist requesting the author to write the document in his or her format, as they are not the expert and should refrain from suggesting changes in style, writing technique, but concentrate on the content. The author of the protocol must realise that the reader is a person, who is often overworked, already has vast amounts of documentation to read and must be enticed to read the protocol as the prime document.

If QA don't understand the document, or the flow of actions, then it is highly unlikely that the site staff would either, and this should be addressed as part of the audit finding.

- (iv) With regard to **ancillary activities**, third party involvement, QA should ascertain from the protocol the clarity of the delegation and, more importantly, an acceptable level of GCP compliance within that third party delegated organisation should be established. If this is

not clear from the clinical trial protocol, then the QA should take up with project management and possibly ascertain this by a visit prior to the start of the study. This is particularly relevant if a new CRO is to be involved.

- (v) Within the protocol, there must clearly be a **statement** that the study will be conducted according to good clinical practice and the applicable regulatory requirement, as detailed under ICH GCP 6.2.5.
- (vi) References are also needed for **source documents** and where and what they should be. The identification of data is frequently recorded solely in the case report form, and is often missing, and leads to confusion both from the monitor's point of view and that of the auditor. If the sponsor, CRO and investigator all agree that certain regularly measured and not necessarily safety issue aspects can be recorded in the case report form, there should be a section in the protocol that clearly identifies these, and states that these will be source data as per CRF and no additional recording will be made.
- (vii) Particular attention should be made to the **reporting of adverse and serious adverse events**. There must be a very clear detail in the document relating to how these should be reviewed, reported, timelines and also interaction with IMP. Should a study be blinded, then there must also be a clear paragraph in the protocol covering how the blinding will take place, authority to unblind and procedures and precautions relating to the unblinding.

(In the attached SOP, Section 8.8.3.11 covers in general the evaluation of safety parameters, but the reader should reference the appropriate sections in ICH, the European Union directives and the PV directives and guidelines covering the reporting and dealing with serious adverse events.)

- (viii) **Source documents** and their availability often cause problems for both the auditor and the monitor. Again, this should be discussed at the setting up and initiation of the study, but the protocol should carry a statement that the investigator will allow access to source data and more importantly, that the protocol clearly states that the investigator will allow audit and inspection to take place at any time with access to all source data and relevant documents to substantiate the clinical trial has been conducted in a timely manner, according to the protocol and, importantly, allow access to patient source data.
- (ix) Carrying on from this, the protocol should also clearly indicate that the documents, both source data, medical records and all documentation relating to the patient throughout the lifetime of the study will be retained in a **suitable archive**, or describe an archiving procedure which is acceptable to the site and to the sponsor/CRO for the period of time, as described in the ICH guidelines.
- (x) One point that is always of an issue is **quality control** and checking of data.

There are often pages that are indicated as "statements" from the principal investigator confirming the quality of data, its collection and recording and compliance with GCP. These, from the author's experience, are generally filled out in haste, all on the same day, by the same person who invariably has never seen the study, let alone the documentation, but signs according to the statement "principal investigator statement".

More importantly, the protocol should clearly state that data will be entered and appropriately signed by the person responsible for the data and entering the data. At a suitable period in time, these data will be overseen and supervised by the principal investigator and a signed statement made either in the notes, the source documents or in the appropriate case report form page. There should, however, **be a clear indication that the responsibility for this rests with the principal investigator and it is a task that should not be taken lightly**.

There should also be an indication that should a regulatory inspection take place, this statement will be viewed with the level of authority that it dictates.



- (xi) Within the protocol, particularly in the section regarding **regulatory review** and submission to the ethics committee, it must again clearly state that the study must not start until **written** approval is received from the ethics committee, that appropriate regulatory authority approval again in writing, or in accordance with local standards and regulations has been received, importation documentation where applicable has been received and, most importantly, if applicable, the agreement to the hospital to allow the study to be conducted has all been received in writing, verified by the monitor and is lodged in the trial master file.

**Until this documents and other key “regulatory green light documents” have been received, it is of paramount importance for the protocol to state that no investigational medicinal product (IMP) be shipped to the site. This statement can be qualified in that a third party such as a CRO, import agency, etc., may receive the material in the interim period, but be quite clear that this is not to go into the hands of the investigator until the proviso above has been met.**

- (xii) **Informed consent** should also be very clearly reviewed by QA in the protocol. It must be quite clear that no invasive procedures must take place until the signed consent form has been duly completed by the investigator and patient/volunteer, if there are certain factors where earlier documentation can be used, such as X-ray in the previous 3-month period, MRI in the previous 1-month period, etc., then these should be clearly stated in the protocol and also confirmed in the section on informed consent.

Where routine procedures for the management of the disease take place on a regular basis, these may still be continued without the informed consent of the patient, but it should be quite clear that in no way must these activities be manipulated to include the patient into the study. A typical example would be to add a test for cholesterol, which would not be normally evaluated, should the patient be considered for a study measuring the effect of the drug on cholesterol levels.

- (xiii) The industry is turning very rapidly to **electronic case report forms**, electronic data recording, paperless clinical trials and electronic trials.

These, while still relatively new to the industry, and particularly to the investigator site, must be constructed in compliance with the associated guidance. Computerised systems used in clinical trials (FDA, 1999), for example, recommend that study protocols should identify steps where computerised systems and data will be used in clinical trials.

Electronic signatures and part 11 compliance<sup>2</sup> should also be referred to.

Current industry standards should also be reviewed when putting together protocols, to ensure that the use of electronic data capture, data management systems are compliant with the generally accepted industry standards for these activities, and from QA’s point of view, early audits of these systems must be undertaken to ensure that appropriate validation has taken place, and this is duly documented and approved.

## 2.3 SPECIAL POINTS FOR QUALITY ASSURANCE TO CHECK IN PRE-STUDY DOCUMENTS, SUCH AS THE PROTOCOL, AMENDMENTS AND SUPPORTING DOCUMENTS

- (i) *Studies in Paediatric Populations* – With the recently issued directives and guidelines, QA should check that the protocol clearly states that where these studies are to be undertaken, a specialist reviewer with in-depth knowledge of the disease state in the paediatric population should be present in the ethics committee. This should be written in to the protocol and special care should be taken by QA at the site audit to check if this specialist has reviewed the protocol and is present in the ethics committee membership list. QA

should also review the ICH guidelines on conducting studies in paediatric populations, to ensure that the protocol has the relevant paragraphs to cover these activities.

- (ii) *Comparison of the Protocol with Case Report Forms* – While this will be dealt with later in this chapter, it is of paramount importance to ensure that at the early stages of reviewing the protocol, the draft, or if possible, final case report form documentation is reviewed. Areas that need to be examined are “comments sections” if these are required, are they able to be accommodated by the data management group in the database, is there too little or too much space to allow for comments to be made, and is it quite clear from the investigator point of view what comments should be made. Perhaps QA should review these two documents and suggest that where a comments section has been utilised, it would have been better to put a specific section or series of sections in the case report book.

Other points should be checked to ensure that if actual recording of data is specified in the protocol, there is space for this to be in the case report form. For example, it is often shown in the protocol that three repetitive blood pressure measurements are required. The case report book may only have space for one. This leads the investigator to either carry out only one measurement and perform a protocol deviation or in the worst-case scenario, to take three measurements and report the average.

Another area which is quite complex and confusing is with regard to laboratories. The trend now is to attach the laboratory printout and merely report in the case report book outliers or abnormalities that are of clinical significance, particular variance with the reference range as to require attention to be drawn in the case report book by the investigator. Sometimes, the company requires all of the laboratory data to be transcribed. Additional problems relate to units. The units in the case report book may be at variants with the units reported by the hospital. If the investigator is not aware of this by the time it comes to data management, you could find that severe clinical abnormalities occur that are merely the result of a report being entered into the case report book with one unit, and the case report book having a second unit that gives an inflated or reduced value of clinical significance.

One final point to bear in mind is with regard to vital signs. Unless of paramount importance to the conduct and outcome of the study, height, weight and other demographics, such as male and female, along with vital signs, such as blood pressure, pulse, respiration, *etc.*, may be considered by the doctor as so routine as to enter them directly into the case report form, and not put these in the hospital notes. Once again, reference should be made to the protocol at the time of constructing this to ensure that if these values are of critical importance, and should be in the source notes, they should be detailed accordingly, or the protocol should indicate that these can be regarded as a direct entry into the case report form, and therefore this would be the source.

- (iii) *Amendments* – Amendments to the study protocols are now considered to be a critical issue. Reference should be made to the relevant European directives where an amendment may be considered as a totally new protocol for consideration by the ethics committee. If “a substantial amendment” is submitted (see European Union directive<sup>3</sup>) then it may well have a direct bearing on the timings and approvals. If the ethics committee consider that the amendment is substantial, the study would revert to an original submission and therefore any time spent reviewing the original protocol would be returned to zero and “the clock would start ticking again”. QA should be very vigilant in reviewing amendments and should consider if these are understandable, appropriate in terms of the original reference being cited in the amendment, clear why the amendment is required and how it fits in. QA should also ensure the amendment has been circulated to the original circulation list. They should check the chain of thinking vis-à-vis the investigator being

aware of the changes and whether monitors have explained these amendments to the investigator and relevant site team.

Amendments themselves should be uniquely identified in the sequential manner, have the appropriate header and footer to ensure that these are either draft or final, and most importantly within the trial master file and site file, that these are clearly sent to the ethics committee and appropriate personnel to receive written approval (where applicable).

The changes may impact on the informed consent, especially if changes are safety variables or of a non-administrative nature is required. When a subsequent changed informed consent should be produced, verified, translated where applicable and sent for approval. Notes should be made by QA that this second or third informed consent should be verified at the site audit to ensure that the patient has been given the opportunity to review the change in the protocol since the original informed consent was signed, and confirm whether they wish to continue to take part in the study.

- (iv) *Patient Welfare Groups* – There is an increasing awareness of patient welfare groups, internet groups, *etc.*, in relation to specific topics and clinical trials. QA should pay due credence to whether or not these have been addressed in the protocol or the informed consent, and whether or not there are representatives of this group reviewing the protocol at the ethics committee stage.
- (v) *Compensation and Insurance* – While this is technically not a part of the protocol itself, a paragraph covering insurance must clearly be written and from QA's point of view, at the time of reviewing the protocol, if applicable and possible, the appropriate certificate should be viewed at the sponsor site or by copy from the CRO. QA must pay particular attention to the wording of the insurance certificate to make it abundantly clear that areas where the clinical trial will be carried out, that is countries, are not prohibited in the insurance certificate, that if numbers are a critical factor, that the overall study and its total evaluable population does not exceed the numbers the insurance company have levied on the insurance being valid and that the validity of the insurance either covers the clinical trial period, or that a trigger mechanism is in place to ensure that this adequately addressed prior to the certificate expiring.
- (vi) *Ethics* – Frequently, there would need to be a statement at the beginning of the protocol covering the ethical rationale for conducting the study. It is often a requirement from the ethics committee that this is clearly stated, along with the primary end point to allow them to evaluate the type of study and whether this is ethically viable. The conclusion should clearly be the benefit to risk ratio in the trial is in favour of the subjects and that there is a positive outcome, rather than this to be seen as a possible means to carry out a study for further research benefits. This differs in volunteer studies where there is no benefit (except monetary) to them.

The investigator team should be seen to adhere by the declaration of Helsinki and reference to this is frequently made within the protocol, but it is QA's responsibility to ensure that the most recent version of the declaration of Helsinki is included.<sup>4</sup>

- (vii) *Overview of Clinical Study* – A very useful feature in a protocol is a flow diagram or series of bullet points, clearly indicating what activities will happen at which visit, both for the patient and the principal investigator. It is of vital importance that QA reviews this document and the subsequent sections within the protocol with the overall protocol content. This is an area that is frequently fraught with problems in that either specific items have been missed, overlooked, or not indicated to take place at the same time in all three portions of the document. The overview document is of very great importance to all participants in the clinical study and it is therefore imperative that this provides a true reflection of the study as defined in the clinical trial protocol.

(viii) *Translations* – It is often a requirement that the total protocol, the overview of the project or key elements are subjected to translation. While this is very much sponsor/CRO orientated as to whose responsibility it is, QA should certainly review the translations for the following points:

- Has an adequate translation taken place by defining the document in its original form, through the first translation and the back translation. It is not QA's responsibility to ensure accuracy of the translation, but at least the three steps have been performed.
- Are the header or footer indicating which document relates to which translation, which date and the person performing the translation?
- Can that person be seen in the trial master file or study related files as capable of conducting the translation? Is it necessary to have an official translator and/or are appropriate certificates of translation available? It really depends on the type of organisation and country as to whether an official translator is required, or whether these activities can be conducted by people fluent in a language within the companies concerned.
- Care should be taken that the appropriate translated version is sent to the ethics committee for review – this is particularly important in informed consent, where often a translation takes place; this is sent to and approved by the ethics committee and then subsequently the investigator site makes some minor changes. This is not appropriate and all must be seen by the sponsor company and the official ethics committee approved document is the only one accepted. This is particularly important with regard to informed consents and their translation.

(ix) *Inclusion/Exclusion Criteria* – While it is imperative that QA check the exceptions for consistency between the protocol and the case report form, it is also useful to check the viability of statements. On many occasions, the author has seen the necessity for confirmation of contraceptive methods, pregnancy tests and the non-inclusion of women of childbearing potential when the study is conducted solely in males! This leads to problems with regard to checking the various boxes as to positive actions having been taken with regard to the female inclusion criteria which would then result in the patient being rejected! Care should be taken also in the inclusion criteria where often “cut and paste” from earlier studies have been used, and sometimes the inclusion or exclusion with regard to laboratory values is not always a test that is subsequently being requested to be evaluated. Bearing in mind that this section will satisfactorily allow the inclusion of patients into the study, it is of paramount importance that this section is given particular attention by QA as a viable section – otherwise recruitment will be adversely affected.

(x) *Use of Third Party Sub-Contractors* – While the use of third party sub-contractors and their successful audit is dealt with elsewhere in this book, it is important for QA in reviewing the protocol to make sure that, where applicable, there is continuity between the capability of the third party contractor and the protocol requirements. For example, in a typical imaging study, it may be that the MRI or imaging analysis is conducted by a third party contractor, but documentation and films/electronic data sent to a different organisation in a blinded manner for evaluation. The protocol should clearly describe how this blinding should take place, the precautions to prevent the blind being broken and the logistics for getting the material to the sponsor and back to the investigator in a timely manner. Thus, in a recent study the investigator was to provide initial evaluation of the MRI, while a blinded evaluator was to give the subsequent and official interpretation. This caused major problems: some patients, considered at the investigator site as critical, were not considered by the blinded evaluator. It was unclear therefore as to whose statement should be completed and recorded in the final report, especially where conflicts arose

and no clear statement in the protocol or the study conduct manual explained how these anomalies should be dealt with.

Particularly in this area, the use of central laboratories and local laboratories. It may be that there needs to be a clear distinction that, under exceptional circumstances, the local laboratory may provide the analysis, but again, there must be checks made by QA to ensure that the correct methodology, *etc.*, is in place as these values at the local laboratory may be in variance with the values provided in the main by the contract central laboratory. Assistance may be sought here from checklist (Appendix C) for areas to audit in a laboratory.

Adequate quality control should also be seen as a pre-requisite for evaluating the capabilities of the local hospital laboratory and this should also be covered in the protocol.

## **2.4 COMPARISON BETWEEN THE PROTOCOL AND THE CASE REPORT FORMS**

While this area is of very great importance, it is difficult to describe in detail, as the case report form production varies enormously from company to company and from trial to trial.

The auditor, however, should check key items, to conform protocol requirements are met by CRF pages.

The most important item for QA to ascertain is that at the case report form production stage, there is a clear quality control process and that the key document is the final or draft final protocol. It is a very key element in terms of timelines to ensure that when the protocol is finalised and the study site is initiated, that the case report books are not only available, but printed, translated and found at the site. Therefore, it is too late to carry out a quality control comparison between the case report book and the protocol at this stage. All too often, the author has seen replacement pages being sent and these only lead to problems.

Within the trial master file, there needs to be a clear checking system for QA to review as to who has carried out the quality control, were there involvements of senior personnel, medical monitors, statisticians and even the principal investigator or an investigator advisor. The QA review should ascertain the completeness of the case report books, the subsequent requirements of the protocol to be defined in key areas for completion within the case report book and no anomalies. As has been stated earlier, the free text should be restricted as far as possible as this often leads to major problems of abstraction and compilation of data at the time of producing the database.

QA must ensure the project management team that they are **not proof readers** and it is merely a review, and at best a percentage checking rather than a 100% quality control which must be undertaken by the project team.

QA should finally assure themselves that there is appropriate documentation in the trial master file, including the case report form or book, the authorisation, the suitable translation and, most importantly, the logistics of getting the appropriate documents to the site and signed confirmation of receipt.

## **2.5 QUALITY ASSURANCE INVOLVEMENT IN REVIEWING THE INFORMED CONSENT FORM (ICF) AND PATIENT INFORMATION LEAFLET (PIL)**

These two documents are considered the most important in terms of patient safety and welfare in a clinical trial. An appendix is normally attached to the protocol, what is generally now considered as the “core ICF”. This in general terms means that, at best, this information should be in all of the site ICFs and PILs, but leaves some latitude for local changes to take place.

It is the responsibility of the monitor and the clinical project team to ensure that the ICF/PIL used by the study subject complies with ICH and any additional requirements of the local



regulatory authority, ethics committee or hospital is not conflicting and is acceptable to the sponsor. Therefore, if the core ICF is changed in any way, there must be a clear audit trail tracing this back to an approval by the sponsor and then subsequent translation and submission and approval by the ethics committee.

QA should be active in approving “the core ICF” meets the requirements laid down in the ICH, the European directive and local requirements such as in the UK, the ABPI clinical trial compensation guidelines or the local ethics committee.

Generally, most ethics committees will find the need to change some items in the ICF/PIL. QA must be vigilant when reviewing approvals to ensure that recommendations made by the ethics committee in relation to these documents, and naturally to the protocol itself have been adequately addressed by the sponsor/CRO in writing, changed as an amended document duly noted in the header or footer of that document/documents, and can clearly be seen to have complied with the wishes of the ethics committee. While this is post protocol production, it is certainly a key element of QA review, prior to the start of the study. Once again, a checklist (Appendix D) has been appended to guide the auditor to review the ICF/PIL, but the specific local requirements, clinical trial process and sponsor requirements should be borne in mind throughout.

Key points that should always be addressed by QA are:

- In reading the document, could the auditor as a lay person, understand the terminology, or is it considered that there are items too complex for the average non-scientific person to understand, that is measurement of blood, volumes of blood are frequently unrelated in terms of day-to-day activities for a particular patient.
- Version numbers, dates and page numbers should be as footers or headers, so each version can be clearly identified in terms of submission to ethics committee, translations, *etc.*
- There should be a description of alternative procedures or courses of treatment in line with ICH GCP 4.8.1(i).
- There needs to be consistency and detail regarding adverse events. These again should be checked against investigator’s brochure, and the information leaflet by the QA. Often, many of these are omitted for fear of frightening away the patients or volunteers. They can also be seen by QA as possibly oversimplified or at worst, masked.
- Data protection, allowing access to source documents, confidential review of medical notes by inspectors and qualified auditors should also be adequately addressed in the consent form, and there should be clear sections detailing these each to be signed by the patient so that they are adequately aware of all the activities that will be affording themselves and their data during the lifetime of the clinical trial.<sup>5</sup>
- Specific points relating to local rules and regulations, such as (a) the prevention of storage of plasma samples once a clinical trial has been completed in Scandinavia and (b) the prevention of DNA typing, should be addressed in the consent form with signatures and dates by the patient if required.
- It is useful for the consent form to include a statement either handwritten or added after the ethics approval that “this consent form has been reviewed and approved by the local or hospital ethics committee of hospital x on this date”. This again gives confidence to the patient that the documentation has been reviewed by the responsible body. If this is part of the consent procedure, then QA should check this date with the appropriate approval by the ethics committee and the version number accordingly.
- Timings of consent are now considered to be important and while this is a study-related activity, the QA unit should bear in mind at the time of reviewing the consent form that if this section is available, then at the site they should not only check the time of consent, invasive procedures, the time of receiving IMP and make sure that all of these activities happen post signature, date and time of the patient.

- Translations ensure that the aforementioned details of translations in this chapter have been addressed and that appropriate footers clearly show dates, version numbers and translations; whether it is back translation, original translation, *etc.*
- Specific attention should be paid by the auditor to ensure that where specific types of clinical studies, such as paediatrics, minors, incapacitated adults, *etc.*, all have the consent form and information leaflet, clearly designed in line with the appropriate guidelines to allow signatures to take place by the parent or guardian, a witness being required, an authorised representative of the incapacitated person, *etc.*, and that these all meet not only the local guidelines, but European directive guidelines and directives themselves and that there are adequate spaces to cover these points. QA should also question with the project team that if it is a routine clinical trial, why there is a need for a witness. This is often put in particularly in Eastern European countries or Asian countries and should be queried, as this is not required by ICH unless the criteria mentioned above are part of the clinical trial. If however, it is persistent that a witness is required, then the impartiality of the witness must be examined by QA.

## 2.6 CONCLUSION

As can be seen from this chapter, the involvement of QA at arms length in the production of the protocol, leads to many activities that are integral in the conduct of a satisfactory clinical trial. The interaction between the protocol and case report form has clearly been described. The involvement of QA in reviewing the PIL/consent form, which is part of the protocol is also paramount to ensuring that the patient safety and welfare are maintained according to guidelines and responsibilities of the sponsor.

It is generally considered that involvement of QA in reviewing these critical documents at all stages of its production can only lead to better quality studies, easier transcription in case report books from a meaningful protocol and well controlled, constructive case report forms and that the maintenance and welfare of the volunteer or the patient is clearly covered by the PIL and consent.

## REFERENCES

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2. Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – scope and application; FDA August 2003 ([www.fda.gov](http://www.fda.gov)) (and subsequent revisions).
3. Directive 2001/20/EC of the European parliament and the Council of the 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official journal of the European communities L/21/34 1.5.2001.
4. World Medical Association (WMA) declaration of Helsinki, Ethical Principles for Medical Research involving Human Subjects. Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996 and Edinburgh 2000, with subsequent minor revisions by FDA.
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**APPENDIX A****Protocol Checklist**

<b>PARAMETERS TO BE CHECKED</b>		<b>PRESENT</b>	<b>N/A</b>
<i>General information</i>			
1.	Protocol title <ul style="list-style-type: none"> <li>• Protocol number</li> <li>• Version date</li> <li>• Amendments</li> <li>• Version date</li> </ul>		
2.	Name of sponsor <ul style="list-style-type: none"> <li>• Address of sponsor/monitor</li> </ul>		
3.	Signature page <ul style="list-style-type: none"> <li>• For sponsor</li> <li>• For investigator</li> <li>• For statistician</li> </ul>		
4.	Name and title of person authorised to sign the protocol and protocol amendments for the sponsor		
5.	Name, title, address and telephone number of the sponsors medical expert (or dentist)		
6.	Name of the investigator who is responsible for conducting the trial, and the address and telephone number of the trial site		
7.	Name, title, address and telephone number of qualified physician (or dentist) who is responsible for all medical (or dental) decisions in clinical trial if investigator not medically qualified		
8.	Name and address of the clinical laboratory(ies) and other institutions involved in the trial		
9.	References and appropriate appendices		
<i>Background information</i>			
10.	Name(s) and description(s) of investigational products		
11.	Summary of findings from pre-clinical studies and from other clinical trials relevant to the trial		
12.	Summary of benefits and potential risks		
13.	Description of and justification for the route, dose and regime if administration		
14.	Statement that the clinical trial will be conducted according to the protocol, GCP and the applicable regulations		
15.	Description of the population to be studied		
<i>Trial objectives to be checked</i>			
16.	Objectives and purpose of clinical trial		
17.	Description of primary and secondary end points		
18.	Description of type of trial (e.g. double blind, placebo-controlled)		
19.	Description of measures to minimised/avoid bias		
20.	A description of the trial treatment(s) and dosage form, packaging and labelling of the investigational product(s)		
21.	Description of duration of subject participation including any follow-up period		



22.	A description of discontinuation criteria for subjects		
23.	Accountability procedures for the investigational product(s)		
24.	Maintenance of trial randomisation codes and procedures for breaking codes		
25.	Identification of data to be recorded directly on to CRF's		
<i>Treatment of subjects</i>			
26.	Other treatments and drugs permitted and not permitted during the clinical trial		
<i>Selection and withdrawal of subjects</i>			
27.	Subject inclusion criteria		
28.	Subject exclusion criteria		
29.	Subject withdrawal criteria		
<i>Assessment of efficacy</i>			
30.	Specification of the efficacy parameters		
31.	Methods used for assessing, recording and analysing of efficacy parameters		
<i>Assessment of safety</i>			
32.	Specifications of safety parameters		
33.	The methods and timing for assessing, recording and analysing parameters		
34.	Methods to be employed to produce safety reports and reporting adverse events		
35.	Type and duration of follow-up of subjects after adverse event		
36.	Statistical methods to be used, if any, for interim analysis		
37.	Numbers of subjects planned to be enrolled. Reason for choice, power of the trial and clinical justification		
38.	Level of significance		
39.	Criteria for termination of the trial		
40.	Procedure for accounting for missing, unused and spurious data		
41.	Procedures for reporting any deviations from original statistical plan		
42.	Selection of subjects to be included in the analyses		
<i>Other sections</i>			
43.	Direct access to source data/documents		
44.	Subject identification code list to be kept at the site		
45.	Quality Control and Quality Assurance		
46.	IEC/IRB approval statement		
47.	Data handling and record-keeping <ul style="list-style-type: none"> <li>Planned interim analysis</li> <li>Maintenance of blind planned (separate individuals to those in full analysis)</li> </ul>		
48.	Financing and insurance		
49.	Publication policy		
50.	Is there a table of content and does the pagination match the table		
51.	Do all the instructions make sense and is there consistency		
52.	An information sheet and consent form in appendices		

## APPENDIX B

## LOGO

## STANDARD OPERATING PROCEDURE

## MASTER COPY

Title: PROTOCOL WRITING AND REVIEW

SOP No.:

Version No.:

Effective date:

1. **Objective:** To describe the procedure for protocol writing and process of reviewing the protocol.
2. **Scope:** This standard operating procedure describes the procedures that are followed for preparation of protocol and review so that it conforms as per good clinical practice guideline. It includes all essential elements for conducting clinical trial.
3. **Applicable to:** Project Manager (PM)  
Medical Advisor – Medical & Regulatory Affairs
4. **Attachments:** Attachment 01: Template for protocol title page  
Attachment 02: Protocol review form
5. **Related SOPs:** Nil
6. **SOP Supersedes:** No previous version.
7. **Definitions**
  - 7.1 **Protocol:** A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial.
  - 7.2 **Protocol amendment:** A written description of a change(s) to or formal clarification of a protocol.

	<b>Prepared by</b>	<b>Reviewed by</b>	<b>Authorised by</b>
<b>Name (Capitals)</b>	.....	.....	.....
<b>Signature</b>	.....	.....	.....
<b>Date</b>	.....	.....	.....

8. **Procedures**

- 8.1 Collect all the information required for protocol preparation from medical department or sponsors
- 8.2 Review all the available information relevant to disease and investigational product.
- 8.3 Prepare protocol as per ICH guidelines of good clinical practice to include the all relevant information described below.
- 8.4 The protocol shall be logical and written in simple language such that it can be followed accordingly.
- 8.5 The format of each protocol shall be similar to the format described in this SOP. However, in a CRO situation if sponsors prepare and provide the protocol the sponsor's format will be followed.
- 8.6 An appropriate font of size, minimum "12", shall be maintained for text of protocol. Larger, Bold, Italics and underline font may be used for title, subtitle and text, which are to be highlighted as per requirement.
- 8.7 Header and footer: All pages shall contain protocol no., Version no., Date in the footer. Every page (including title page) shall be numbered individually with total number of pages in respective protocol in footer.
- 8.8 **Structure of protocol (see relevant ICH section)**
  - 8.8.1 Title page and first page should contain the following
    - Protocol identification number and trial reference
    - Date-effective/amended
    - Version

- Title of protocol in bold and all capitals (and short title if applicable)
- Name and address of sponsors
- Name and address of CRO (if applicable)
- Name of approval personnel, Medical Director, Vice-President, Statistician, PI, *etc.*
- Third party address (if involved)
- Details of all responsible trial personnel
- Study summary
- Confidentiality statement: The protocol shall carry a confidentiality statement in italics style “*Confidential & proprietary – This document contains information proprietary to The Company. The unauthorised use, disclosure, distribution or copying of these information is strictly prohibited.*”

8.8.2 **Table of contents:** describes the content of that protocol as per given template describing serial no, title, subtitle and page number.

### 8.8.3 **Content of protocol**

8.8.3.1 **List of abbreviations and definitions of terms:** A list of the abbreviations, and lists and definitions of specialised or unusual terms or measurement units used in the protocol should be provided. Abbreviated terms should be spelled out and the abbreviation indicated in parentheses at first appearance in the text.

8.8.3.2 **Study overview and trial design with flow chart:** A brief overview that summarises the protocol should be provided.

8.8.3.3 **Introduction:** Briefly describe the background about the disease leading to the proposed work. It should be concise and include the significance of this study, and why the results of the proposed work may be important. Include why the proposal is likely to produce new and useful information, or is related to fundamental problems. Background details about the IMP and related safety and efficacy trials should also be included here.

8.8.3.4 **Objectives:** State the primary objective, plus any secondary objective with its rationale. This portion should be no longer than one short paragraph. If there is more than one primary objective they should be described as above.

8.8.3.5 **Study design:** This shall describe the kind of study proposed. Describe the phase of study. Will there be a control group? How will the decision as to which patient will get the treatment, *i.e.* randomised or not be made? Will blinding be part of study? If not, why? Whenever possible, the protocol should be design the in such a fashion that neither the study subjects nor anybody who has any contact with them have any knowledge of the study group assignment. Give the justification for design of the study if blinding or randomisation is not performed or any specific design is included. The number of subjects to be screened to give an effective evaluation number should be the result of discussions with the statistician.

### 8.8.3.6 **Patients and methods**

- **Entry criteria:** Inclusion and exclusion criteria.  
Factors to consider as criteria for patient inclusion and exclusion:  
Characteristics of patients
  - Sex and precautions for avoiding pregnancy
  - Age range
  - Weight
  - Medical history exclusion, *i.e.* duration of disease
  - Race and/or ethnic background
  - Life expectancy if applicable

- Use of tobacco; ingestion of caffeine and/or alcohol
- Abuse of alcohol and drugs
- Performance status (WHO coding)
- Physical status and any biological requirements (enzymes at particular levels, *etc*)
- Surgical or anatomic limitations
- Hypersensitivity to a clinical trial medicine or test
- Other medicine and non-medicine allergies
- HIV Status
- Previous or current involvement with clinical trial material
- Ability and willingness to give consent.

Characteristics of the disease and its treatment

- Disease being evaluated – onset and severity, *etc*.
- Concomitant medicines – allowed and/or forbidden
- Previous medicine and non-medicine treatment
- Washout period of non trial medicines or non-medicine treatments
- History of other diseases
- Present clinical status
- Previous hospitalisations
- Enzyme of biochemical/haematological restrictions.

Environmental and other factors

- Patient recruitment and willingness to participate
- Written informed consent for all trial procedures
- Any other criteria in the opinion of investigator may influence the study result, compliance of the patients or harmful to patients.

- **Subject withdrawal criteria and rules for early clinical trial termination:** for individual subjects, parts of trial, and entire trial and procedures specifying:
  - When and how to withdraw subjects from the trial/ investigational medicinal product (IMP) treatment.
  - The type and timing of the data to be collected for withdrawn subjects.
  - Whether and how subjects are to be replaced.
  - The follow-up for subjects withdrawn from IMP/trial treatment.
  - When and how to terminate part of a trial or entire trial.
- **Screening procedure and enrolment**
- **Randomisation procedure**
- **Blinding procedure**
- **Deviations from protocol or waivers from sponsors.**

8.8.3.7 **Investigational Medicinal Product (IMP):** This section shall provide the information regarding IMP.

- Name
- Formulation
- Labelling
- Distribution and storage

- Control of Clinical Trial Material
- Supply, logistics, regulatory green light approval
- Shipment and logistics
- Onsite accountability
- Re-labelling (expiry)
- Destruction
- Drug compliance
- Drug administration: Dosage, regimen, route of administration and treatment period.
- Concomitant medication
- Interaction with other drug
- Any relevant information available for conducting clinical trial.

8.8.3.8 **Patients visits:** This section shall describe the detail of patients visit required and procedure to be done during each visit.

8.8.3.9 **Endpoints**

#### **Primary endpoints**

- This section shall describe specific outcomes identified to help assess the performance of the clinical trial depending upon the hypothesis being evaluated. Primary endpoint needs to be specific and to be easily evaluated. The outcomes specified in this section should correspond to the outcomes that are used to calculate the sample size and statistical analysis.
- The outcome measure used for treatment comparisons will be a clinical event (*e.g.* death, myocardial infarction, significant loss of vision, recurrence of a disease) or a surrogate outcome measure (*e.g.* a score on a psychological test, blood pressure change, serum lipid level).
- Desired characteristic of the primary outcome measure
  - Easy to diagnose or observe
  - Free of measurement or ascertainment errors
  - Capable of being observed independent of treatment assignment
  - Clinically relevant
  - Chosen before the start of data collection.
- Outcome characteristics

#### **Secondary endpoints**

These sections shall describe the additional parameter other than primary endpoints, which are being evaluated and relevant to particular clinical trial (*e.g.* safety parameter, epidemiological data, quality of life assessment. *etc.*).

8.8.3.10 **Response evaluation:** This section shall describe the proposed tests, methods or procedures sufficiently detailed, and well defined to allow adequate evaluation of the primary and secondary endpoints.

8.8.3.11 **Safety evaluation:** This section shall describe

- Definition of adverse events and serious adverse event
- Methods of recording and assessing adverse events
- Procedure for reporting serious adverse events including contact number and address for reporting SAE of sponsor and/or CRO responsible persons. Times and annual reports to IEC.

- Monitoring of the patients with adverse event.
- Over dosage and intoxication with investigational product.
- Coding and results and database entry/responsibility.

8.8.3.12 **Statistical consideration:** This section shall describe the following

- Patient population suitable for evaluation – sample size calculation
- Sample size estimation
- Analysis plan: Interim analysis, Final analysis and any other relevant timeline to be mentioned
- Parameter and statistical methods proposed to be used for efficacy, safety and any other analysis.
- Statistical software (if applicable).

8.8.3.13 **Ethical aspects**

- GCP and protocol compliance: A statement that the trial will be conducted in compliance with the protocol, ICH GCP, Indian GCP and applicable regulatory requirement(s).
- Informed consent: Process of informed consent to be described
- Patient insurance coverage: Plan for insurance coverage for patients to be described.

8.8.3.14 **Verification**

- Monitoring
- Audit from QA
- Inspection from competent authorities (CA).

8.8.3.15 **Data management**

8.8.3.16 **Evaluation for analysis**

- Intention to treat
- Per protocol evaluation

8.8.3.17 **Trial termination**

- Interim analysis
- Planned end of trial
- Premature termination of trial

8.8.3.18 **Responsibilities (third party)**

- Data management
- Contractors
- Central laboratories
- X-ray/MRI
- IVRS

8.8.3.19 **Reports and publications**

8.8.3.20 **Retention of clinical trial documentation**

8.8.3.21 **References:** In the text of protocol reference number is inserted at the end of a sentence in a square bracket. References are to be compiled at the end of

the text and must be listed and numbered in the order in which they are cited in the text. They should be type written under the heading "References". Abbreviations for titles of medical periodicals should conform to those used in the latest edition of *Index Medicus* and on Medline.

**Reference style should be maintained as shown in following example:**

- Journal article with one, two, or three authors:
  1. Dolan ME, Pegg AE: O-Benzylguanine and its role in chemotherapy. Clin Cancer Res 1997, 8(2):837-847.
- Journal article with more than three authors:
  2. Knox S, Hoppe RT, Maloney D, et al: Treatment of cutaneous T-cell lymphoma with chimeric anti-CD4 monoclonal antibody. Blood 1996, 87(8):893-899.
- Journal article in press (manuscript is in the publication process):
  3. Scadden DT, Schenkein DP, Bernstein Z, et al: Combined immunotoxin and chemotherapy for AIDS-related non-Hodgkin's lymphoma. Cancer (in press)
- Supplement:
  4. Brusamolino E, Orlandi E, Morra E, et al: Analysis of long-term results and prognostic factors among 138 patients with advanced Hodgkin's disease treated with the alternating MOPP/ABVD chemotherapy. Ann Oncol 1994, 5(suppl 2):S53-S57,
- Book:
  5. Iverson C, Flanagan A, Fontanarosa PB, et al: American Medical Association Manual of Style 1998 (ed 9).Williams & Wilkins, 883-887

8.8.3.22 **Tables:** This section will contain relevant information required in tabulated form and numbered in the order in which they are cited in the text.

8.8.3.23 **Figures:** This section shall contain figures required in protocol and numbered in the order in which they are cited in the text.

8.8.3.24 Any other additional information may be added as appendix.

8.8.4 **Signature:** Signature page for CRO/Sponsor contains the Name, place for signature and designation of author/(s) and approval authorities. Signature page for investigator contains the statement agreeing to conduct clinical trial in accordance with protocol, GCP and Declaration of Helsinki along with place for name of investigator, date and signature.

8.8.5 A copy of declaration of Helsinki

8.9 After draft protocol prepared it will be reviewed by expert in that particular therapeutic area or person with experience in clinical trial to be identified by The Company.

8.10 A copy of protocol stamped as draft copy will be provided to reviewer after obtaining confidentiality agreement.

8.11 Review process shall be documented in the protocol review form. (Attachment 03)

8.12 Any suggestion from sponsor, investigator and reviewer will be sought and appropriately incorporated.

8.13 After completing the review process protocol will be finalised. Signature of author and approving authorities shall be obtained.

**APPENDIX C****Local Clinical Laboratory Checklist**

<b>PARAMETERS TO BE CHECKED</b>		<b>PRESENT</b>	<b>N/A</b>
<i>Facilities</i>			
1.	Suitable size:		
2.	Designated areas for: <ul style="list-style-type: none"> <li>• Receipt:</li> <li>• Administration:</li> <li>• Analysis:</li> <li>• Disposal of waste:</li> <li>• Storage of samples:</li> <li>• Separate microbiological isolation:</li> <li>• Radioactivity studies:</li> </ul>		
3.	General conditions: <ul style="list-style-type: none"> <li>• Air-conditioned:</li> <li>• Clean:</li> <li>• Sufficient incubators:</li> <li>• Sufficient freezers:</li> <li>• Sufficient refrigerators:</li> </ul>		
4.	Disaster planning: <ul style="list-style-type: none"> <li>• Emergency generator:</li> <li>• Equipment in duplicate:</li> <li>• Comparison between parameters on duplicate equipment:</li> <li>• Frequency of comparison:</li> </ul>		
5.	Sub-contractors: <ul style="list-style-type: none"> <li>• What parameters or tests:</li> <li>• Responsibilities defined in a written document:</li> </ul>		
<i>Personnel</i>			
6.	Name of director of laboratory: <ul style="list-style-type: none"> <li>• CV available:</li> </ul>		
7.	Evidence that the technicians are trained and supervised: <ul style="list-style-type: none"> <li>• CVs available</li> <li>• Training records:</li> <li>• Rotation of staff on different apparatus:</li> <li>• Contract staff used:</li> </ul>		
8.	Staff signature sheet: <ul style="list-style-type: none"> <li>• Up-to-date:</li> <li>• Initials:</li> <li>• Responsibility:</li> <li>• Date of signature:</li> </ul>		



<i>Equipment</i>			
9.	Calibration records: <ul style="list-style-type: none"> <li>Available from (year):</li> </ul>		
10.	Maintenance records: <ul style="list-style-type: none"> <li>Available from (year):</li> <li>Contract for external maintenance:</li> <li>Records of external contractors available:</li> <li>SOP for maintenance and calibration available:</li> </ul>		
11.	Emergency power supply: <ul style="list-style-type: none"> <li>What equipment can operate:</li> </ul>		
12.	Temperature monitored in: <ul style="list-style-type: none"> <li>All incubators:</li> </ul>		
	<ul style="list-style-type: none"> <li>All freezers:</li> <li>All refrigerators:</li> </ul>		
<i>Computer systems</i>			
13.	Validation documentation available: <ul style="list-style-type: none"> <li>Certificates of validation from vendors:</li> <li>Maintenance and repair by internal group:</li> <li>Maintenance and repair by contractors:</li> <li>Back-up every (hours/days):</li> </ul>		
<i>Investigator packages</i>			
14.	Bottle samples and containers: <ul style="list-style-type: none"> <li>Supplied to sites (outside hospital sites usually):</li> <li>Needles supplied:</li> <li>Ice and packaging:</li> <li>Labels prepared:</li> <li>Any QC:</li> </ul> Method of transport to the laboratory:		
<i>Chemical reagents</i>			
15.	All reagents labelled: <ul style="list-style-type: none"> <li>Correct label:</li> <li>Date of preparation (if appropriate):</li> <li>Date of destruction:</li> <li>Documented procedure for removal of reagents due to expiry date of reagent:</li> </ul>		
16.	Water quality: <ul style="list-style-type: none"> <li>Source of water:</li> <li>De-ionized:</li> <li>Distilled:</li> <li>Tested for impurities:</li> </ul>		
17.	Location: <ul style="list-style-type: none"> <li>Comprehensive:</li> <li>Authorised by senior member of staff:</li> <li>Date of last review:</li> <li>Effective date of use:</li> <li>Manuals for equipment available:</li> <li>SOP on SOPs:</li> </ul>		

<i>Quality control</i>			
18.	Internal QC: <ul style="list-style-type: none"> <li>• Written internal QC procedures:</li> <li>• Standards and controls used in appropriate frequency:</li> <li>• Stated tolerance limits:</li> <li>• Written procedure if beyond limits:</li> </ul>		
19.	Accreditation/certification documents: <ul style="list-style-type: none"> <li>• Names of authorities:</li> <li>• Date of last inspection:</li> <li>• Date of expiry:</li> <li>• Nature of inspection (health aspects of staff and facility or review of laboratory procedures):</li> </ul>		
<i>Flow of samples</i>			
20.	Reception of samples: <ul style="list-style-type: none"> <li>• Samples transported by hospital staff:</li> <li>• Samples transported by other means:</li> <li>• Bar-coded on arrival:</li> <li>• Log book available:</li> <li>• Recorded on a database:</li> <li>• Distribution from reception area to analyser by:</li> </ul>		
21.	Analysis of samples: <ul style="list-style-type: none"> <li>• Written criteria for rejection of samples:</li> <li>• Written procedures for out-of-range samples:</li> <li>• Written procedures for review of results:</li> <li>• Delta checks (comparison with previous results):</li> </ul>		
22.	Reference ranges: <ul style="list-style-type: none"> <li>• Source:</li> <li>• Appropriate for study (age, race, sex):</li> <li>• Written procedure for revising reference ranges:</li> <li>• Method of informing new reference values to investigator and sponsor:</li> </ul>		
<i>Specific to project</i>			
23.	Head of laboratory has: <ul style="list-style-type: none"> <li>• Protocol:</li> <li>• Contract with sponsor and/or CRO:</li> <li>• Contract for sub-contractors:</li> <li>• Documentation describing responsibilities to sponsor:</li> </ul>		

24.	Reporting of results: <ul style="list-style-type: none"> <li>• Sent to investigator by (fax, paper, <i>etc.</i>):</li> <li>• 24 hour service (if appropriate):</li> <li>• Procedure for reporting parameters out of range:</li> <li>• Time from detection to reporting of “alert” values:</li> <li>• All results reviewed before dispatch to investigator/sponsor:</li> <li>• Results to be entered into CRFs by hand:</li> <li>• Order of parameters in CRF and units same as laboratory report sheet:</li> <li>• Data sent to sponsor database electronically:</li> <li>• Report contains reference ranges:</li> </ul>		
<i>Archiving</i>			
25.	Specimens: <ul style="list-style-type: none"> <li>• How long kept:</li> <li>• Facility where kept:</li> <li>• Written procedures describing the archiving:</li> </ul>		
26.	Documentation: <ul style="list-style-type: none"> <li>• How long kept:</li> <li>• Facility where kept:</li> <li>• Written procedures describing the archiving:</li> </ul>		
27.	Electronic data: <ul style="list-style-type: none"> <li>• How long kept:</li> <li>• Facility where kept:</li> <li>• Written procedures describing the archiving:</li> </ul>		

## APPENDIX D

PARAMETERS TO BE CHECKED		PRESENT	N/A
<i>Essential features</i>			
1.	Title of protocol on front page:		
2.	Version, date and pagination with total pages (e.g. x of y pages):		
3.	Identification of subject (e.g. subject initials and date of birth):		
4.	Will the ICF be translated, country-specific?		
<i>Statements of the following should be present</i>			
5.	Trial involves research:		
6.	Identification of the study drug to be used in the clinical trial and the therapeutic class:		
7.	The reason for doing the research:		
8.	Trial treatment and the probability for random assignment to each treatment (if appropriate):		
9.	The trial procedures including any invasive action:		
10.	The responsibilities of the subject:		
11.	Those aspects that are considered experimental:		
12.	Reasonably foreseeable risks or inconveniences (side effects) to the subject and, when applicable, to an embryo, foetus or nursing infant: <ul style="list-style-type: none"> <li>Same risks or inconveniences as described in the protocol and investigator brochure:</li> </ul>		
13.	Particular treatment may involve risks to the subject which are at present unforeseeable:		
14.	The reasonably expected benefits:		
15.	Alternative procedures or other treatments that are available to the subject and their risks and benefits:		
<i>Statements of the following should be present</i>			
16.	Compensation and/or treatment available to the subject in the event of trial-related injury:		
17.	Any anticipated payment based on involvement in clinical trial (prorated):		
18.	Anticipated expenses:		
19.	Person(s) to contact for further information with respect to the clinical trial and the rights of trial subjects and whom to contact in the event of trial-related injury:		
20.	Foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated:		
21.	Circumstances and reasons for the termination of the subject's participation in the trial may be terminated:		
22.	Expected duration of the subject's participation in the trial:		
23.	Approximate number of subject's involved in the clinical trial:		
24.	Subject has had sufficient time to ask any questions and to have them answered in a satisfactory manner:		
25.	Participation of the subject in the trial is voluntary; he/she can refuse to participate or withdraw anytime without penalty:		

26.	Permission of the subject will be obtained by the investigator before the personal physician is informed of the participation of the subject in the study:		
27.	The language is non-technical and can be understood by the subject or his/her representative:		
28.	The language implies no guilt or blame on the subject ( <i>i.e.</i> exculpatory):		
29.	Direct access to the medical records (charts) for monitors, auditors and regulatory authorities providing the subject or his/her representatives authorised such access by signing the consent form:		
30.	Any records or documents identifying the subject will be kept confidential:		
31.	Subject will be informed of any new developments that may effect the agreement of the subject to continue in the clinical trial:		
32.	Copy of the whole ICF with signatures and dates will be provided to the subject/legally acceptable representative:		
33.	Sufficient space for signature of study subject or legally acceptable representative and date:		
34.	Space for a signature and date of the person who took part in the discussions with the subject concerning the informed consent:		
35.	Any special requirements in the study where additional information and agreement required, <i>e.g.</i> HIV test:		
36.	Appropriate special consent process and consent form(s) when a child or person who is mentally or physically unable to give written consent:		
<i>Data Protection Act (European Union only)</i>			
37.	Name of the drug company or institution:		
38.	Purpose of processing the clinical data:		
39.	The categories of recipients for whom the data may be disclosed:		
40.	Explanation that the subject has the right to be given access to his/her data so as to confirm that it is correct:		

## CHAPTER 3

# Standard Operating Procedures in the Good Clinical Practice Environment

P. CHARNLEY NICKOLS AND J. NICKOLS

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Consideration of quality systems is a common feature of GCP inspections performed by most of the European regulatory authorities, and the FDA is increasingly pursuing such an approach. The FDA already places considerable emphasis on its review of pharmacovigilance systems.

When an inspection or audit of GCP quality systems is performed, the inspector or auditor will usually begin by reviewing the standard operating procedures (SOPs) of the organisation under consideration. This is because SOPs are intended to be a written statement of the quality procedures of the organisation.

The SOPs are an essential part of the GCP quality system. Their roles in compliance with GLP and GMP are discussed in Chapters 16 and 27, respectively.

### 3.1 WHAT ARE SOPs?

The SOPs describe systems and/or processes. Simply, they document the ways of performing an activity or achieving an objective.

SOPs are a fundamental part of a company's quality management system, which also includes audit, training and quality control. They also form a part of the document hierarchy which, in Europe, consists of Regulations, Directives, national legislation, national and international guidelines (*e.g.* ICH), company policies, SOPs, manuals and study of specific work instructions or guidance. In the United States, Federal and State legislation occupy the roles of the first three categories.

### 3.2 WHAT DOES GCP REQUIRE IN TERMS OF STANDARD PROCEDURES?

ICH GCP (1.55) defines SOPs as “Detailed, written instructions to achieve uniformity of the performance of a specific function.”

Section 2.13 of ICH GCP goes on to state that ‘systems with procedures that assure the quality of every aspect of the trial should be implemented’.

Companies should review the precise wording of these two sections carefully. GCP clearly rules out the use of SOPs that represent vague statements of intent. It states that SOPs should be *detailed*. It also states that SOPs should be set out in *writing*.

Section 5.1.1 on “Quality Assurance and Quality Control” states further “The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with

written SOPs to ensure that trials are conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).”

Traditionally, SOPs were contained in bulky folders and the issue of revisions and additions represented a major physical exercise, quite literally, with the production and distribution of multiple paper copies. Many companies are now turning towards the use of electronic SOPs for routine circulation, although most still retain an original approved master copy on paper. There are considerable advantages and disadvantages to both approaches and these are discussed later in this chapter.

### **3.3 WHAT ARE THE PURPOSES OF SOPs AND WHAT ARE THE COMMERCIAL AND OTHER BENEFITS TO THE COMPANY OF HAVING GCP COMPLIANT SOPs?**

SOPs provide the link between requirements – regulatory, statutory, contractual and policy – the theory of clinical research, with their practical interpretation and implementation in a company setting. They should be applied to routine core activities that can be standardised.

In the past, the production and administration of a GCP compliant SOP set was often viewed by management as unnecessarily bureaucratic and an impediment to productivity. Those required to implement the provisions of SOPs often expressed the view that they inhibited initiative and detracted from the pleasure of the work. Fortunately, these views are becoming less prevalent and both staff and management appreciate that SOPs deal efficiently with detail and enhance creativity and independence in a more secure environment. SOPs improve efficiency, boost productivity and prevent useless and sometimes inadequate duplication of effort in establishing methodology and training material. Protocols can refer to SOPs rather than detail the procedures. They also help to ensure that production of compliant and comprehensive documentation is an integral part of any process and not regarded as an unnecessary additional burden.

There are clear advantages to the establishment of readily accessible, user friendly, agreed set of procedures in clinical research.

Firstly, SOPs provide evidence to inspectors of the procedures in place, which lead to the generation of a set of clinical data. They permit reconstruction of events, and thus it is important that they be sufficiently detailed and that out-of-date SOPs are archived. Auditors and inspectors will appreciate the addition to each trial master file of a list of applicable SOPs for the duration of the study.

Secondly, SOPs can be the “shop window” of a company’s quality systems. They are a clear statement of the company’s commitment to quality standards and set out the precise methods by which compliance with these standards is to be achieved in the specific company environment. This demonstration of the existence of well-controlled quality systems provides reassurance to management and others. The content of the SOPs is of course critical, but almost equally important in terms of impression are the format and lay out of the SOPs, how approachable the content is, the efficiency of the system of administration of the SOPs and the amount of priority given to GCP quality systems as evidenced in the resourcing of the SOPs system.

Even with the most efficiently run and comprehensive SOP system, of course, the ultimate implementation of the quality procedures is dependent on the knowledge and commitment of the clinical research staff themselves. During a quality system review, staff will be interviewed and given the opportunity to demonstrate these qualities. It is important to emphasise that inspectors do not expect verbatim recollection of precise SOP wording, but rather an impression of understanding of the principles and philosophy, and an evident commitment towards compliance. The ability to access detailed instructions rapidly is seen as a demonstration of knowledge of and familiarity with the quality management system.

Thirdly, SOPs should, and indeed are required to, ensure standardisation of procedures. This enables management to set standards and ensure regulatory compliance and compliance with company policies both within and between individual departments and also, in the case of international companies, across the gulfs of geography and cultural practices that sometimes separate individual operating companies. Purpose and outcome sought should be stated. Outcomes allow assessment of effectiveness and permit objective measurement of success.

SOPs are not intended for the untrained naïve personnel. They should be designed for the users' degree of education and experience, without making inappropriate assumptions of prior knowledge or memory. Uncontrolled processes waste far more time, energy and expense. SOPs reduce variability and errors. By following an effective SOP, the same result can be achieved irrespective of operator, time or location. Results can then be compared and combined for regulatory submission.

Finally, SOPs provide an invaluable platform for staff training and support. The processes of SOP production and review are excellent training opportunities in themselves and involvement in these processes boosts staff motivation. They are a support to training but not an alternative. However, SOPs may give greater insight at all levels. They involve accountability, set out company requirements, policies and standards, confirm knowledge, clarify responsibilities and dispel false assumptions. By making processes and responsibilities transparent, they can highlight unreasonable demands on individuals or groups.

SOPs should be accessible to staff at all times for reference and self-training and should be used as the basis of corporate training in all aspects of clinical research. It is important to realise that good SOPs in themselves do not remove the need for other forms of training. Inspectors will seek evidence of process-specific training in individuals' training documentation and in the knowledge of the processes demonstrated during the course of interviews and review of clinical research data and documentation.

### **3.4 WHOSE ACTIVITIES SHOULD BE GOVERNED BY SOPs?**

ICH GCP 2.13 clearly states that all aspects of the trial should be the subject of quality procedures.

Within the pharmaceutical industry, this means that SOPs and SOP training applies to all those who perform tasks that in any way impinge on clinical research, whether in sponsor companies or contract research organisations (CROs). This must include at least the following staff: medical writers, project managers, statisticians, data managers, monitors, pharmacovigilance staff, clinical trial supplies manufacturing and handling staff, file managers and archivist, IT staff, trainers and quality assurance (QA) staff.

Companies vary widely in their approach to the organisation and division of their SOPs and SOP topics. Traditionally, each department has set up its own SOPs, dealing discretely with its own functions and with little by way of overlap or links with the SOPs of other departments. However, pharmaceutical work flows between departments. One department acts as the supplier of another, which is in effect its customer. The workflow is not uniform or unidirectional.

ICH E 8 guideline General Considerations for Clinical Trials points out that the traditional division of clinical research into four numbered phases is simplistic and that in practice, several phases including pre-clinical testing may be ongoing at any one time. Thus, it is important to ensure that all the company SOPs interlock precisely like a jigsaw, leaving no areas uncovered, no areas of uncertainty and no areas of conflicting responsibilities or approaches.

The use of cross-functional SOPs represents an approach for satisfying these requirements.

#### **3.4.1 Cross-Functional SOPs**

Cross-functional SOPs consider the inputs in the form of materials, procedures, methods, information and/or people (skills, knowledge, manpower and training). These may come from "suppliers"



in the same functional area, different departments or company locations or even external sources. The SOPs then address the activities of the “processor” or SOP user in producing the output, which can take the form of products, services, information and/or documentation. This output is supplied to the “customer” or recipient who again may be in the same functional area, different departments or company locations or even external bodies.

SOPs for pharmacovigilance may provide a good model of cross-functional SOPs. Input will be information and reports supplied from a variety of sources including health professionals, company staff and general public. This information is processed to provide outputs in the form of reports to government regulatory bodies, corporate and affiliate regulatory departments, investigators, ethics committees and project teams. The suppliers, processors and recipients must all be clear about their responsibilities and the standards to which they must work in terms of timelines, accuracy and completeness of information.

Inputs, processing and outputs must meet specifications set out in the SOP, and the responsibilities for all relevant parties regardless of departmental divisions are clearly indicated. Thus, cross-functional SOPs are used by staff from several functional groups. They may, however, be supplemented by single-function SOPs.

### 3.4.2 Single-Function SOPs

These may be used for discrete functions or to supplement cross-functional SOPs in terms of those responsibilities that are exclusive to the department. Thus, monitoring, data entry, computer validation, statistical analysis can all be subjects of single-function SOPs even though each forms a part of the larger system of data acquisition and processing.

### 3.4.3 Cross- vs. Single-Function SOPs

The cross-functional approach may result in fewer SOPs. It should enhance harmonisation of activities and reduce the probability of gaps and overlaps in procedures. Staff may gain increased job satisfaction from a clearer view of the importance of their role in achieving a particular objective. However, such SOPs are complex and may take longer to develop and agree on. Approval is required from all functions involved and similarly all functions require near-simultaneous training on issue or revision. A strong cross-functional coordination role is required in order to establish and maintain such a system.

Single-function SOPs can usually be developed faster than cross-functional SOPs. It is quicker and easier to train staff in a single department and implementation should be easier. These SOPs already fit within the company structure, they tend to be shorter and simpler and they require fewer approvals. However, companies with single-function SOPs typically have more SOPs, and extra care is required to harmonise them and to avoid gaps and overlaps. In terms of company culture, such SOPs can reinforce isolationism and separation of functions.

## 3.5 SOP TOPICS AND SCOPE

Table 1 sets out some suggestions for SOP topics and the scope of the SOPs required by most companies to be implemented as part of the quality management system.

The topics that must be covered by SOPs vary depending on the nature of the company and its business. Virtual companies will need to place a heavy emphasis on SOPs dealing with sub-contracting and monitoring of suppliers. Large all-round pharmaceutical companies will require a full range of SOPs. Specialist CROs will require a discrete subset. The test is to consider whether all routine activities, *i.e.* those that recur and can be standardised, are addressed.

Outside the pharmaceutical industry, ICH GCP (Section 3.3) requires independent review boards and independent ethics committees to “establish, document in writing, and follow . . . procedures”

**Table 1** Topics and scope of standard operating procedures

<i>Topic</i>	<i>Scope</i>
SOPs, protocols, CRFs, consent documentation, reports	Documentation production, formatting, administration, distribution and control, revision, archiving and destruction
Files and archives	Selection, administration, maintenance, security, access
Use of contractors	Selection, approval, contracts, oversight, audit, termination of contract
Hardware and software systems and other equipment	Development/acquisition, validation and testing, installation and verification, user acceptance, training and use, security, system maintenance and support, database administration, document control, problem resolution, change management, backup and recovery, archiving and retrieval, retirement and migration, review and audit
Human resources	Training, finance, information systems, records and document tracking
Project management	Planning, ongoing management, close-out activities
Pre-study	Study design Study approval Development and approval of Protocol, case report forms, diary cards, investigator brochure, consent documents Regulatory application, communication and approval Ethics committee application, communication and approval Investigator and site selection Laboratory selection Contract research organisation (CRO) selection Agreements Investigator Institution CRO Laboratory Pharmacy Indemnity and insurance Financial disclosure Randomisation and code breaking Structure, content, preparation, maintenance and storage of study files
Study initiation	Initiation visits to sites, CROs, laboratories, pharmacies
Monitoring	Patient recruitment, payment to volunteers, monitoring visits, laboratory procedures, source document verification, ongoing review of study data
Study completion	Study close-down activities at all relevant locations, archiving of study documentation
Data management	Database planning and entry, clarification and query resolution
Pharmacovigilance	Pre- and post-marketing
Investigational medicinal product (IMP)	Requisitions, labelling and packaging, distribution, accountability, recall
Fraud	Detection and handling of suspected fraud
Quality assurance (QA)	Organisation of the QA department Training of QA auditors QA SOP administration QA documentation and filing

*(Continued)*

**Table 1** (Continued)

<i>Topic</i>	<i>Scope</i>
	Planning QA audits Conducting QA audits Study documentation Study locations Study results and reports Company systems External contractor systems Reporting QA audits Follow up of responses to QA audit findings
Statistics	Analysis plans, assessment of eligibility and evaluability, database lock, unblinding, data listings, analysis and summary tables, statistical report
Reports	Final integrated study reports, regulatory submission, approval and release of final reports
Administrative	Training and training records Personnel files Security Health and safety Cleaning Power failure Office procedures Company structure and administration Subcontracting, contract negotiation, requirements, acceptance criteria, monitoring and closure Financial administration Advertising and promotion External relations

and the guidelines go on to indicate which procedures should be included. ICH GCP is silent on the subject of the use of SOPs for investigators but does require the investigator to comply with GCP, the study protocol and any other agreed contract and these documents must comply with the sponsor company's SOPs.

### 3.6 HOW SHOULD SOPs BE MANAGED?

Ideally, SOPs should be written by those who will use them. They should reflect current practices and comply with applicable regulations, guidelines and policies. They should be produced to a standard format, which clearly identifies each document in terms of title, date and version number. It is recommended that pages are numbered in the format “page  $x$  of  $N$ ”, where  $x$  is the page number and  $N$  is the total number of pages in the document. This reassures the reader that the document is completed.

Approval by senior management should be clearly indicated and some consideration should be given to what “approval” really means. Ideally, the dated approval signature should be accompanied by a printed identifier and an approval statement.

Each SOP should include the date of approval or release and an effective date, the date from which the procedures should be implemented. It is difficult to support the situation where these two dates are identical, except in the case of minor revisions to an existing SOP. In the case of new SOPs or those subject to major revision, common sense requires some familiarisation or training time before implementation.

The SOP management system should include regular and timely routine reviews and provisions for premature review and revisions when required. Security systems should be in place to prevent unauthorised modification of SOPs and circulation to unapproved parties. Circulation should be monitored, and there should be a system of recall and archiving for out-of-date versions.

Each SOP should clearly define responsibilities and tasks – what is to be done, under what circumstances, when (and how frequently), where and by whom, *e.g.* “the clinical research manager will accompany the first site visit performed by each new monitor”, and not that “some monitoring visits may be performed jointly” (*by whom and when not stated*).

### 3.6.1 Sources of Information for SOPs

The following should be consulted in order to determine the content of an SOP:

- Regulations for the relevant jurisdictions
- Guidelines (GCP – EU, FDA, WHO, Canadian, Australian or any other relevant guidelines)
- Company policies
- Other company SOPs
- Company SOP on SOPs
- User’s own knowledge and experience of the process and those of colleagues
- Interfacing departments or sections
- Management and QA
- Technical and practical information available – published manuals, instructions or hand-books

### 3.6.2 Stages in the Development and Life of an SOP

Most SOPs will go through all of the following stages during their life cycle. Table 2 indicates these stages, the party who is usually responsible and some points to consider at each stage.

### 3.6.3 SOP Format and Contents

The company should have an SOP on SOPs that describes the company standards for the format and main sections of any SOP. In many cases, the SOP on SOPs will provide, in itself or as an appendix, a template to be followed in the production of any SOP.

The following sections should be considered for inclusion in any SOP (Table 3):

### 3.6.4 Paper and Electronic SOP Systems

Increasingly, companies are considering and implementing electronic systems to administer, produce and distribute their SOP sets. The disadvantages of paper SOP sets include ecological and economic considerations such as the number of copies required to be produced and distributed, the heavy, bulky folders which contain them, cumbersome administration, handling and use. Individual copies and volumes are usually numbered and logged on issue, written receipts are retained and recalled superseded copies are collected, re-logged and destroyed. Sometimes owners state that existing SOPs are lost. Should these versions resurface at a later date, there is the danger they are used instead of the most recent version.

*3.6.4.1 The Challenges of Electronic Standard Operating Procedure Systems.* Electronic SOPs while providing many advantages also have associated problems. One cannot assume the use of electronic SOPs will improve compliance. Just as for paper, staff members need incentives

**Table 2** *Stages in the development and life of a standard operating procedure*

<i>Stage</i>	<i>Responsibility</i>	<i>Comment</i>
Identify need	User/manager/other	
Assign authorship	Manager/SOP administrator	
Collate information	Author	Focus on commonly agreed aspects initially and then deal with disputed areas
Organise information	Author	
Draft	Author	Clearly and accurately – correct sequences without gaps, test whether it works
Review	Author/user/manager/other	Is the process described compliant? Is the SOP user friendly, logical, complete, correct and practical?
Review	SOP administrator/committee	SOP consistency of contents and format, avoidance of gaps and duplication, smooth workflow, identification of flaws, SOP compliance with legal requirements, guidelines, company policies and standards
Modify and finalise	Author	
Approve	Manager	Specify what approvers mean when they approve – compliance, avoidance of gaps and duplication, smooth work flow
Produce	SOP administrator	SOP numbering, format, consistent use of glossaries and abbreviations, keywords
Distribute	SOP administrator	Control and record distribution, file and archive master copies, archive superseded version
Receive	User/other SOP holders	Destroy/return old versions
Use	User	

and opportunities to read and use them. They do not entirely achieve the objective of eliminating SOP-related paper files and, in the absence of a validated system of electronic signatures, may still require authorised paper master copies. Some users may prefer the mobility and accessibility of paper, and printed versions may be needed where computer accessibility is not possible. Under these circumstances, most companies implement a system that adds a printed “expiry” date to printed copies and a flag indicating that printed copies are not to be relied upon as current ones.

Electronic SOP systems require controlled internal, national and/or international network distribution or, perhaps for laptop users, distribution on electronic media such as floppy disks and CDs. The former system requires development of a system with adequate access speed and convenient points of access. The latter system requires prompt provision of updates and periodic checks to ensure that correct versions are in use. Additional computer equipment may be required, and IT support is essential in the form of “Help Desks” and hardware and software support. System and network reliability are critical, and there must be arrangements for access in the case of failure. If access fails, staff members are discouraged and will be reluctant to use the system in future.

**Table 3** Sections considered for inclusion in any standard operating procedure

Title page		
Table of contents		
Introduction	Objectives, scope, basis	Clear statement of the purpose of the SOP Indication of the extent of its applicability Applicable policies, regulations and/or official guidelines, principles
Applicability	Departments, sections and roles given responsibilities in this SOP	Use standard company job titles
Definitions and abbreviations	Alphabetical list to aid user	Use standard company terms and abbreviations Explain acronyms and technical terms
Process map	Flow diagram, Gantt chart	Indicate processes graphically or pictorially in logical sequence with responsibilities indicated at each stage
Procedures	Step-by-step sequence of what, when, where and how to achieve	Simple clear format Logical procedural order Suggest use of numbered sections and/or bulleted points, diagrams and supplementary flow charts Active tense Cover usual and exceptional cases For every stage indicate who should be consulted and who is responsible for carrying out the process
Documentation	Documents to be gathered Documents to be generated and distributed Records of conversations and contacts Filing and archiving	Information required in order to carry out each procedure – indicate source of information Information to be produced as part of the procedure – indicate recipient of information Letters, faxes, e-mails, telephone conversation records required to be maintained During the process and on completion
Related procedures	Cross references	Interactions with other SOPs
Change history	Cumulative audit trail	Changes since previous version and rationale for change
References	References and sources	Explanation and justification for the process and additional supportive information Provides clear separation of supplementary information and explanations from instructions
Exhibits	Forms, examples, checklists	Examples and templates of documents Documentary evidence of a compliant procedure

The system must be validated (Chapter 37) as part of the quality management structure and when software or hardware is updated, there will be a need for coordination throughout the user network to ensure maintenance of services.

Security can be an issue. The possibility of deliberate or accidental corruption by users or others must be minimised. Access to the system may involve passwords and other restrictions may be employed such as security firewalls, virus protection and encryption.

An electronic SOP user guide must be produced, and staff will require electronic SOP system training.

**3.6.4.2 Some Advantages of Electronic SOPs.** Apart from elimination of paper handling, electronic SOPs offer many advantages and new opportunities:

- An integrated approach and access to SOPs, forms and templates.
- A system for distribution and online work through drafting, reviewing, approval, finalisation, *etc.*, *i.e.* throughout the document life cycle. The system can accommodate current and former versions as well as those under review and in draft SOPs. These must be clearly identified and segregated with restricted access and functional permissions for various roles.
- User comments and suggestions can be readily submitted and collated.
- The system may issue alerts when reviews are due.
- Special copies can be annotated with comments during the drafting and reviewing process.
- Automatic number allocation and version control to ensure the version available is always current. This can be a problem in ongoing studies, so there must be provision for access to superseded copies if the decision has been made to delay updating for a particular study – automatic numbering and version numbering.
- Fast, controlled and logged distribution.
- Rapid access to current SOPs throughout the company both locally and internationally.
- Audit trails and usage records. It is possible to monitor the frequency and duration of access, provide linked training and identify which SOPs are most used and for the longest and which are difficult or slow to use.
- Use of attachments and training aids.
- Possible interactive training at the most relevant times.
- Navigation tools and search mechanisms for keywords, use of hyperlinks, automatic index generation, links to relevant forms and templates.
- Interesting, dynamic formats.
- Electronic archiving.

### 3.6.5 Some Additional Points on SOP Content

Short SOPs are more encouraging to the reader, who finds them less daunting and is less likely to lose interest. Avoid information overload – do not include unnecessary or irrelevant detail or information. Keep it brief and clear and well presented.

An index, table of contents and, in the case of electronic SOPs, relevant and efficient hyperlinks will be appreciated by the users and will encourage consultation and compliance.

Where a process is repeated, use nesting and iteration and re-use standard text.

Use the present tense, imperatives and “must”. “Shall” and “should” may be misinterpreted as “you can if you wish”.

Avoid requirements for subjective judgements. Words such as “reasonable”, “relevant”, “appropriate”, “if necessary”, “when applicable”, “take into account” and “consider” obviate the objective of the SOP, which is to create uniformity of performance.

When the SOP has been drafted, talk through the procedures detailed and ensure that there are no omissions or ambiguities.

Remember that each SOP must serve the needs of a wide range of users – senior to junior, experienced to those in training and in some cases such as pharmacovigilance and project management, from many functions.



### 3.7 REVIEW OF SOPs

SOPs must be living documents. In order to be compliant, they must be reviewed regularly and modified as required to reflect changes in regulations and guidelines, ethics, technology and company structure. The frequency of review should reflect the degree and rate of change in these factors and there should be opportunity for unplanned modifications in case of urgent need.

Companies should encourage contributions and suggestions from users, “customer” and “suppliers” of the process and such suggestions should be integrated into the SOP review system. It is important that those making such a contribution should receive thanks and reasoned feedback about how the idea is or is not to be used.

Many companies undertake annual review of their SOPs, but the timing as well as the frequency of SOP review requires consideration.

If all SOPs are to be reviewed simultaneously, then there are important workload considerations surrounding how this can be managed while sustaining normal company business activities. Simultaneous review, however, has the advantage of permitting re-alignment and integration of several processes at the same time.

Staggered review, say relating to the birth date of each SOP, may be logistically easier to handle but provides neither the same united focus nor such ease as part of continual overall process improvement.

### 3.8 SOP COORDINATION

The roles of any SOP committee, SOP coordinator and the QA function of the company are fundamental in this area and should themselves be clearly specified in SOPs. Responsibilities for all of the following should be allocated:

- Compliance with legal requirements, guidelines, company policies and standards
- Numbering and version control
- Consistency of contents and format
- Links with other SOPs
- Avoidance of gaps and duplication within and between SOPs
- Smooth workflow
- Flaws, impracticalities and conflicts
- SOP history log
- Consistency of responsibilities and job descriptions
- Appropriate review
- Correct and timely approval
- Controlled, recorded distribution, return and destruction of superseded versions
- Filing and archiving of master and historic copies
- Groupings and sub groupings of SOPs
- SOP directories/catalogues
- Keywords
- Consistency of definitions, abbreviations, acronyms and company functional names
- Accessibility at point of use.

### 3.9 TRANSITION TO NEW SOPs

Change management is a science in itself. When developing new SOPs or modifying existing ones, it is essential to maintain a clear view of the objective of the SOP. An SOP coordinator or committee should be involved in implementation of the planned change, keeping control and maintaining



consistency of objectives. Changes should not be made without proper consideration of effects on the overall strategy and structure of the company, other associated systems, the users, “suppliers” and “customers”, the training and skills required, timelines and costs.

Those responsible for the all stages of production, review and approval of the new SOP should be clear about any former established procedures and the precise areas of proposed change. They should specify the new procedures and responsibilities precisely. New or modified forms, templates and other documentation may require drafting.

Any training issues should be identified, including who requires training, the areas and types of training required, who should deliver the training and the timing of any training to be undertaken.

The impact on existing work, studies ongoing during the change period, should be considered. This will have an impact on the decision as to when the new procedures should begin to be implemented, the last possible date for implementation and whether implementation should be simultaneous or staggered. It should be determined at what point the QA unit may begin assessment of the degree of enhanced compliance resulting from the new procedure.

### **3.10 SOP COMPLIANCE, MONITORING AND THE APPROACH TO NON-COMPLIANCE**

SOPs are useless if the content is not known, *i.e.* they are not read and if they are not followed. The accessibility and portability of the procedure will affect the probability that it is read. Ready electronic access or the production of pocket-sized subsets of the full SOP volume increases the likelihood that the SOP will be consulted and enhances compliance.

SOPs require an authority. This may take the form of regulations and thus the law, but should also arise from the internal authority of management, which is responsible for the staff members who implement the procedure. Company policy should state that users require the consent for any deviation from a very senior level. In addition to management in an enforcement role, management attitude and commitment are vital factors. It is important that the management demonstrates clear support of SOP initiatives by both direct involvement and the facilitation of required resources.

SOP effectiveness must be assessed by monitoring, QA audit and inspection and by encouraged feedback from “suppliers”, users and “customers”.

There are many reasons why non-compliance with SOPs may occur. Some of these may seem familiar and some may occur in combination.

Staff members:

- Disagree with the SOP
- Do not understand the SOP
- Have not read the SOP
- Find it inconvenient to consult the SOP
- Do not realise the importance of SOP compliance
- Do not recognise the risks/penalties of non-compliance
- Have not received the necessary training
- Have not had time to absorb and apply new or revised SOPs
- Are resistant to change

Compliance is enhanced by a feeling of ownership, enthusiasm, acceptance of the need, confidence and the efficiency and ease of use of the procedure. Involvement, consultation, appreciation of contributions, adequate explanations and training and sufficient time are key influences on the acceptance of and compliance with a new SOP.

### 3.11 SOP TRAINING

ICH GCP makes it clear that it is necessary but not sufficient to provide a compliant set of SOPs. As one of the basic principles of GCP, Section 2.8 states “Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s)”. Section 5 goes on to place the responsibility on the sponsor to ensure that individuals involved in all stages of the clinical trial process are qualified and trained.

Documented evidence of appropriate training is required if compliance with these requirements is to be claimed and this should be available in the form of up-to-date training records, CVs and job descriptions (Chapter 39).

SOP self training has been a common approach, but it is often felt that SOPs are boring and it is hardly encouraging for a new member of staff to be presented with the full volume of SOPs and be told to read them.

Modern computer-based training and assessment modules relating to SOP knowledge, interpretation and application can obviate the tedium of the task, but they must be well designed and depend on availability of appropriate technology.

Face-to-face teaching and discussion is the best way to ensure full understanding and commitment. Interactive exercises and scenarios, games and quizzes provide a stimulating platform for training and staff development.

Properly trained individuals feel that they are able to develop their full potential and contribute to the success of the company. They are aware of improved personal performance and better quality work. Uncertainty, waste and errors are reduced, and job satisfaction and commitment are enhanced.

In order to have suitable training programmes available at the correct time, *i.e.* after approval and before implementation of new procedures, it is essential that the trainers are involved from an early stage in new developments. This enables them to make the necessary careful preparations of training material, training personnel, venues and schedules. Clearly, the area of training and SOP training in particular should itself be the subject of SOPs!

SOP training should be focused on specific groups if it is to be well received and effective. Specific functional areas may require training on a particularly relevant new or modified SOP, or its applicability may be geographically regional or international. Different levels of staff up to and including senior management may require different approaches in terms of intensity, rationale, practical detail and regulatory implications. The scope and ownership of each SOP are critical in determining its training requirements.

### 3.12 WHO SHOULD OWN THE SOPs?

The importance of the commitment to SOPs, which arises from a sense of ownership, has already been discussed. However, in a world of increasingly international commerce, determining the scope and ownership of SOPs is not always easy. Here we consider the advantages and disadvantages of the use of corporate, internationally applicable SOPs compared with SOPs that are locally owned and applicable.

#### 3.12.1 Corporate SOPs

Corporate SOPs are often produced in order to achieve standardisation and clarity of procedures across international company borders. They simplify the process of SOP training as the same procedures and same training programmes are universally applicable. They also facilitate the transfer of staff to different areas of the world as this can be achieved without complex retraining and familiarisation. It is difficult to use corporate SOPs to fit all local situations.

### 3.12.2 Local SOPs

Local SOPs are often required in order to achieve compliance with local regulatory requirements and practices. They may be associated with an enhanced feeling of ownership and control as the local staff may have been more closely involved with their production and approval. They may also result in better understanding of processes as local language and phraseology can be employed in their drafting. Care must be taken to ensure that local SOPs from one part of the company harmonise with those of other parts of the company and that the procedures undertaken produce compatible and comparable results.

### 3.12.3 Mixed Local and Corporate SOPs

In practice, most companies arrive at a compromise between entirely local and entirely corporate SOPs and as a result gain some of the advantages and, unfortunately, also some of the disadvantages of both systems.

This compromise can be achieved in a variety of ways:

- Corporate SOPs with local sub-sections
- Corporate SOPs with local appendices. This type of SOP is simpler than the above and involves a degree of local ownership
- Corporate SOPs and separate sets of local SOPs.

The first two approaches result in each SOP being a single document that accommodates both local and corporate requirements, but such SOPs are difficult to keep updated and complicated to produce and use. They cover both local and corporate requirements and have the advantage that all sections of the company are aware of the existence and detail of specific local requirements.

The third approach produces both local and corporate ownership and address local and corporate requirements in detail. Again, such SOPs are difficult to keep updated and complicated to produce. They are particularly difficult for the user who has to consult and amalgamate the requirements in both documents. They do not provide local insight into all other areas of the company.

### 3.12.4 Sponsor and CRO SOPs

In a situation where the sponsor subcontracts some or all of its trial-related duties and functions to a CRO, it is a matter of contractual specification as to which set or subset of SOPs should be used.

All CROs are required under ICH GCP Section 5.2.1 to have systems of QA and quality control, which imply the requirement for SOPs. It is essential for sponsor companies to assess the CRO SOPs to determine whether they meet company standards and regulatory requirements. ICH GCP Section 5.2.1 reminds the sponsor that the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

In addition to the determination of which SOPs will be applicable during the contract, the sponsor must also assess whether there are any associated training requirements for operational staff and how compliance with SOPs will be monitored during the contract.

## 3.13 WHAT ARE THE MOST FREQUENT PROBLEMS CONCERNING SOPs?

The most frequent problems concerning SOPs are as follows:

- SOPs do not cover all aspects of clinical research. Statistics, IT and personnel are examples of functional groups that frequently have an underdeveloped set of SOPs. Procedures may be in place, but are not formally stated and may be handed down by “word of mouth”. In some cases, “gaps” in procedures are seen where the SOPs of one functional area do not exactly meet those of another, leading to apparent breaks in responsibility and/or audit trail.

- A standard format for SOPs is stated, but some SOPs do not comply.
- SOPs do not include a clear date and/or version number.
- The implementation date of an SOP precedes the latest date of approval.
- Approval of an SOP is by an unidentified person, an unauthorised person or is omitted altogether.
- The authorisation procedure is not set out. Those approving have no clear guidance about what they should check.
- There is no waiver or violation policy.
- There is no requirement for users to sign a compliance statement and no contractual SOP compliance requirement.
- SOPs have not been reviewed recently, or there is no evidence of recent review and there is no review policy or procedure.
- SOPs are out of date and do not reflect current requirements and/or actual performance of procedures.
- Users have no input to SOPs.
- Poor access to SOPs is either through an electronic system, such that SOPs are inaccessible due to shared use of computer terminals, or during activities where no computer access is possible. Bulky paper SOP sets are not available during out-of-house activities.
- Unauthorised paper printouts of electronic SOPs are in use and not in control.
- Paper-based SOPs are inaccessible. They may be stored in a position that inhibits access, for example the supervisor's office, or a single copy may be shared between a department with no backup copy when the original is in use.
- The archived set of SOPs is incomplete and/or difficult to relate to periods of study activity.
- There is no formal SOP administration system or SOP on SOPs and no distribution list.
- There is a lack of resource for SOP development and administration.
- Referenced attachments and forms are missing or inadequate.
- There are internal conflicts within and between SOPs in terms of procedures and responsibilities.

### 3.14 SOP ESSENTIALS – A SUMMARY

Essentials of SOPs are summarised as follows:

- SOPs must be in place.
- The range of topics covered by the SOPs should achieve compliance with Section 2.13 of ICH GCP as stated above, *i.e.* all clinical trial procedures are covered within the scope of the SOP set.
- The content of each individual SOP must comply with national law and regulations, with GCP and any other applicable guidelines, *e.g.* GMP for investigational medicinal products or other ICH guidance notes, and with any statements of individual company policy.
- SOPs should be internally consistent and consistent with other SOPs within the SOP set.
- SOPs should be sufficiently detailed so that an appropriately trained and qualified person could reproduce procedures on the basis of the information supplied. However, in order to achieve practicality, there must be a balance between sufficient and too much detail.
- SOPs should be up to date and reflect current practice. Thus, they must be feasible and practical and subject to regular review and revision. Ideally, they should be written and owned by those who perform the procedures described, but if this is not the case, then the operators' input and review should be sought.
- Responsibilities for performance of procedures described should be unambiguously allocated.

- SOPs should be agreed upon and supported by senior management. Management has a responsibility to ensure that all necessary procedures are documented and applied.
- Appropriate SOP compliance should be a requirement for all involved in clinical research.

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## CHAPTER 4

# Preparing for Regulatory Inspection of Company Pharmacovigilance Systems and Practices in the European Union and United States

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## 4.1 INTRODUCTION

There are significant differences in how inspectors from the US Food and Drug Administration (FDA) and those from the regulatory agencies in the European Union carry out their respective mandatory inspections of industry pharmacovigilance systems and practices. However, these distinctions arise from regulatory variation rather than differences in overall goals or approach. As a result, for the many companies working in the pharmaceutical and biological product sectors that have entities marketed in both geographical regions, a common strategy for preparing these inspections is appropriate, particularly with FDA and EU inspections not limited geographically to the region covered by the respective agencies. For companies operating in these regions but without inter-continental markets, this strategy is still relevant and appropriate: by virtue of this preparation, there will be assurance that pharmacovigilance in the company concerned is supported by quality systems, processes and procedures. These are surely in the best interests of the company, its products and, ultimately, patients.

In this chapter, we set out what a pharmaceutical (drug and/or biological product) company [in the United States, holder of an approved new drug application (NDA) or abbreviated NDA (ANDA), or licensed biologics manufacturer (see below regarding marketed prescription drugs for human use without approved NDAs)]; in the EU, “marketing authorisation holder” needs to do to comply with the regulations and regulatory guidelines on pharmacovigilance in the United States and the EU. In using the term “pharmacovigilance”, we include safety surveillance on marketed products and all the associated regulatory and scientific activities. However, the chapter also considers serious adverse event (SAE) reporting from clinical trials. The chapter draws on our experience as former regulators and as company employees, and more recently as consultants carrying out voluntary audits on behalf of companies in the United States and Europe.

It is proposed that there are three elements in preparing for pharmacovigilance inspections.

- The prior implementation of quality systems and processes covering all aspects of safety surveillance
- Preparation for process of inspection
- Remediation of findings following inspection (and hence preparation for likely re-inspection).



The first of these is a major and complex undertaking and will accordingly be considered at length in this chapter. It should not be confused with the second element, which merely ensures that the inspection process is facilitated. Even given substantial notice of intended inspection, this time is insufficient to do much to remedy fundamental failures in systems and processes. As what can be achieved is necessarily limited, so this second element is relatively briefly presented. Corrective actions following inspection are necessarily focused on the details of the findings in the company concerned; although there are some common threads, this section will also, of necessity, be relatively short.

It should be pointed out that, while processes for handling adverse events in clinical trials may be inspected as part of a Good Clinical Practice (GCP) inspection, this may also be examined as part of a specific pharmacovigilance inspection. It is the latter that is the subject of the present paper: although there is an overlap with clinical trial GCP inspections, these are not covered in depth here.

## 4.2 REGULATORY BACKGROUND

### 4.2.1 European Union

In the European Union, the principal regulations concerning pharmacovigilance are EU Regulation 726/2004<sup>1</sup> for products authorised by the Centralised Procedure (superseding Regulation 2309/93 in November 2005) and Directives 2004/27<sup>2</sup> (amending Directive 2001/83 in November 2005) for nationally authorised and Mutual Recognition authorised products. For safety in clinical trials, the main legislation is the Clinical Trial Directive, 2001/20.<sup>3</sup> At the time of writing the respective regulatory guidelines are Volume 9 of the Rules Governing Medicinal Products in the EU<sup>4</sup> and the Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports arising from Clinical Trials on Medicinal Products for Human Use.<sup>5</sup> However, EU Directives are implemented by enactment in law in each of the Member States, and these local laws are therefore also applicable at a national level.

In addition to the placing of obligations for pharmacovigilance on marketing authorisation holders, the regulations also require certain actions by the regulatory authorities and provide them with powers accordingly. Specifically, Article 104 of Directive 2004/27 states that: “Member States shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties”. It also states: “Such inspections shall be carried out by officials representing the competent authority that shall be empowered to: . . . inspect the premises, records and documents of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX, and in particular Articles 103 and 104”. These latter refer to pharmacovigilance requirements. At the time of writing, a draft EU Regulation has been published by the European Commission for purposes of consultation regarding the nature of the penalties to be applied in case of regulatory non-compliance.

### 4.2.2 United States

In the United States, the principal regulations for pharmaceutical pharmacovigilance are

- (i) 21 CFR 310.305 [records and reports concerning adverse drug experience (ADEs) on prescription drugs marketed for human use without an approved NDA (the so-called “grandfathered” products) – under 310.305, manufacturers, packers and distributors all have ADE reporting responsibilities].
- (ii) 21 CFR 314.80 (post-marketing reporting of ADEs in human drugs with approved NDAs).
- (iii) 21 CFR 314.98 (post-marketing reports of ADEs and record keeping per 314.80 requirements on drugs with approved ANDAs) – *i.e.*, generic drugs.

- (iv) 21 CFR 600.80 [post-marketing reporting of adverse experiences (AEs) with biological products] – regulation essentially identical to 314.80.<sup>6</sup>

As explained in the FDAs “Chapter 53 – Post-marketing Surveillance And Epidemiology: Human Drugs: Enforcement of the Post-marketing ADE Reporting Regulations”, a September 30 1999 guidance to FDA field staff that is publicly available on the FDA website,<sup>7</sup> the post-marketing ADE regulations apply to both prescription drugs and over-the-counter (OTC) drugs with approved applications, including those which undergo a switch from initial marketing as a prescription drug under an approved application to OTC status.

Regarding pre-marketing clinical trials, 21 CFR 312.32 (Investigational IND safety reports) covers reporting of ADES for both drugs and biologics under investigation.<sup>6</sup>

It is under these applicable regulations that FDA enforces company compliance with ADE/AE reporting and related activities through inspections.

### 4.3 ACTIVITIES OF THE INSPECTORS

#### 4.3.1 European Union

In Europe, inspectors from national regulatory authorities carry out inspections on behalf of the EU Member States and, for centrally authorised products, on behalf of the EMEA (European Medicines Agency). European inspectors may also carry out site visits in non-EU countries, and have been known to inspect corporate offices in the United States. Most of the experience to date has been with inspections carried out by the UK MHRA (Medicines and Healthcare Products Regulatory Agency) and the Netherlands MEB (Medicines Evaluation Board), but there have also been inspections by inspectors from the regulatory authorities of Portugal, France and Ireland. It is usual for two or more inspectors to carry out a pharmacovigilance inspection, with the visit to company offices lasting 4 or more days.

The performance of pharmacovigilance inspections in the EU is covered by the Position Paper on Compliance with Pharmacovigilance Regulatory Obligations issued by the (then) Committee for Proprietary Medicinal Products (CPMP) in 2001.<sup>8</sup>

The guidelines indicate that the scope of the regulatory obligations – and hence the activities that are subject to inspection – include expedited reporting; periodic safety update reports (PSURs); response to requests for safety information from regulatory authorities; handling of urgent safety restrictions and variations; continuous monitoring of safety; notification of changes to benefit/risk; fulfilling safety commitments previously made to regulators; and performance of internal audits. The guidelines also refer to scrutiny of standard operating procedures (SOPs), the need for accessibility to the safety database within the EU, and confirmation that the company has a Qualified Person for Pharmacovigilance for Europe.

With regard to expedited reporting, the guidelines refer to both the timing of submission of case reports and their quality, as well as to the adequacy of procedures for follow-up of individual cases. Documents that inspectors may use to check on the adequacy of submission of expeditable cases include interim and final post-authorisation study reports and PSURs. Requirements for PSURs are mentioned at length, with the implication that compliance with these will be checked. Reporting of adverse reactions and submission of interim and final study reports from post-authorisation safety studies are also the subject of inspection.

At the time of writing, a new guideline – Monitoring of Compliance with Pharmacovigilance Regulatory Obligations and Pharmacovigilance Inspections<sup>9</sup> – is about to be incorporated in the new Volume 9A EU pharmacovigilance guidelines. The new guideline indicates that, in addition to carrying out inspections, the regulatory authorities should monitor the following for compliance with pharmacovigilance regulations: the appointment of the EU Qualified Person for

Pharmacovigilance; the availability of pharmacovigilance data; immediate notification of change to product benefit-risk; expedited reporting of adverse reactions; periodic safety update reports; responses to requests for information from the competent authorities; submission of safety variations; the fulfilment of commitments made to the Committee for Medicinal Products for Human Use (CHMP) for Centrally-authorized products; and reporting from post-authorisation safety studies.

The new guideline indicates that inspections may be carried out as a routine. Alternatively, targeted inspections may be triggered by a variety of factors unrelated to specific concerns, such as lack of a previous inspection, first product on the market in Europe, a merger or takeover or a new safety system at the company. Other triggers include specific concerns about product safety or non-compliance with pharmacovigilance requirements having been observed. Inspections may focus on pharmacovigilance systems, personnel and facilities, using products as examples to test the system, or may focus specifically on a given product, if relevant triggers were identified. Inspections may also be carried out at the facilities of any party carrying out pharmacovigilance activities on behalf of the company concerned.

Based on the recent experience of pharmacovigilance inspections carried out in the EU, companies may expect some or all of the following, depending on the nature of the inspection (routine or for cause) and on the regulatory authority concerned. In an opening meeting, an inspector provides an overview of the scope and plan for the inspection. There is initial examination of documentation, including SOPs, and review of quality systems – for example, processes for generation and control of SOPs, and auditing practices. The safety database will be explored at length, including examination of validation documents, change control, backup, security, maintenance and disaster recovery procedures. There may be a request to see data entry being carried out, and probably a request for specific data to be produced – for example, reproduction of a previously performed search of the database, or generation of a specified line-listing of cases.

The way that the Qualified Person for Pharmacovigilance for Europe performs his/her role will be explored in detail. Indeed, there may be a check made on the out-of-hours availability of the QP or a suitable deputy. The inspectors will also probably examine job descriptions, *curricula vitae* and training records for other staff working in pharmacovigilance. Interviews should be anticipated between the inspectors and the Qualified Person, pharmacovigilance staff at all levels, training staff, quality assurance and compliance personnel, staff working in Information Technology in support of pharmacovigilance, medical information and library staff, those working in marketing and sales (including field force representatives), regulatory affairs personnel, clinical research/medical services staff, those working in product complaints/quality and archivists. Interactions between the pharmacovigilance department and staff in these various departments may come under scrutiny.

The inspectors will review various elements of pharmacovigilance documentation including sight of specified ADR reports and corresponding source documents. Assessments of expectedness and seriousness as well as compliance with expedited reporting may be examined. Inspectors will look at individual cases and compare data held on the case in the safety database with that present in source documents and submitted regulatory reports. Arrangements for case closure, record filing and archiving are also candidates for scrutiny by inspectors. In particular, there may be questions about record retention and the physical security of unique records.

Processes for regular screening of the medical and scientific literature for adverse reaction reports and handling of adverse events from all other sources, including SAEs from clinical trials and medical information enquiries, will be investigated. Of particular interest to the inspectors is the relationship and contractual arrangements for pharmacovigilance activities between the Marketing Authorisation Holder and those third parties that are concerned with marketing or distributing the products.

PSURs come in for particular scrutiny, with review of the production process, procedures, timetables for production, timing of submission as well as examination and deconstruction of individual PSURs, looking at format, contents and the handling and reporting of individual constituent cases.

The way signals are detected will also probably be subject to inspection. This might be extended to include a request for sight of minutes of corporate safety committee meetings, even if these take place outside the EU.

Following a closeout meeting where the inspectors present their key findings, there is likely to be presentation of a draft report within some weeks. An opportunity is provided for the company to disagree with the inspection findings, provided that there is evidence available to refute these. After some possible negotiation, there will be issue of a final report. Following this, the company will be expected to submit plans for remedial action, together with a commitment to carry these out within a specified time frame.

### **4.3.2 United States**

Activities of the FDA inspectors regarding compliance with ADE/AE reporting obligations are similar to those of EU inspectors, with a few differences:

- (i) As PSURs are not yet mandated by FDA [NB: the FDA's 2003 Proposed Rule on "Safety Reporting Requirements for Human Drug and Biological Products", which specifies the transition from "traditional periodic safety reports" (TPSRs) to PSURs,<sup>10</sup> is not yet final], TPSRs rather than PSURs are examined, unless a company has obtained agreement from FDA to submit PSURs instead.
- (ii) There is no Qualified Person in the United States.
- (iii) The FDA's Proposed Rule represents the agency's current thinking on clinical safety and post-marketing pharmacovigilance, but as it has not yet been finalised (and may indeed undergo significant revision before it is), its basis for inspectional/compliance activities is questionable.
- (iv) Just as until recently there was no European equivalent to the FDA's Inspectional Guidance, there is no individual FDA equivalent to the EU's Position Paper on Compliance with Pharmacovigilance Regulatory Obligations, which spells out specific regulatory obligations subject to inspection.

However, as so many pharmaceutical companies are multi-national, a fair number of pharmacovigilance compliance auditors (both internal and external) have chosen to perform audits in non-EU regions (including the United States, Australia and other areas) based on current EU standards.

## **4.4 ESTABLISHING QUALITY SYSTEMS AND PROCESSES COVERING ALL ASPECTS OF SAFETY SURVEILLANCE**

The essential elements that need to be in place are:

- A validated, adequately functioning safety database and associated systems
- Appropriately experienced and trained staff
- Processes for identifying, receiving, recording, assessing, handling, distributing and storing reports of adverse events/reactions from all relevant sources
- Processes for reviewing the accumulating safety data on products, including those derived from studies, identifying signals, making decisions and taking any necessary action to inform regulators and others and to protect patients
- Processes for generating, reviewing and submitting the requisite periodic reports
- Arrangements for responding to safety enquiries from regulatory authorities
- Established responsibilities and lines of communication, quality assurance, quality control, metrics and audit to support all of the above.

The specific requirements for each of these will now be discussed. It should be appreciated that the requirements will differ in scale and in detail depending on the organisational structure of the company and whether we are considering a global or regional headquarters or an affiliate/subsidiary office.

#### 4.5 THE DATABASE AND ASSOCIATED SYSTEMS

There is a need for a database that fulfils the following functions:

- Recording of details of adverse events, with delineation of initial and follow-up information
- A browser or auto-encoder that supports the use of MedDRA<sup>®</sup> for data entry
- The ability to track adverse events received in respect of dates and actions carried out
- Reproducible production of line listings and tables for periodic reporting, signal detection and safety reviews and summaries
- Capability for searching for cases according to defined parameters
- Production of case reports in appropriate format for expedited reporting and other purposes.

If companies who market products in the United States, or perform clinical trials there, chose to maintain their records or submit designated information electronically, they become subject to requirements specified in 21 CFR Part 11: Electronic Records; Electronic Signatures. However, the requirements for Europe are less certain: while the EU regulators do require validated databases, it is less clear what exactly is needed.

For EU purposes, validation probably requires the following:

- A detailed description of the data model and algorithms used
- Documented procedures for data entry and retrieval
- Controlled access to data entry and retrieval limited to specified individuals
- Control and recording of any changes
- Demonstrable reproducible generation of data.

Validation documentation will need to be available for inspection and should include user requirements, validation master plan, installation qualification, operation qualification and user acceptance testing.

An audit trail is needed, as may be the capability to retrieve versions of the database frozen at different time points. Either the system needs to accommodate the numerous E2B data fields and support electronic transmission, or it must be capable of supporting – either by uploading XML files or by duplicate entry of data – the Internet-based WebTrader system.

What is clearly vital to the effective operation of the system is the availability of sufficient, suitably trained, IT support staff that understand the needs of pharmacovigilance.

For Europe at least, it has not been established whether, for companies that receive only occasional reports of adverse events in any year, there is a regulatory requirement for a fully validated and functioning database. It might be that a paper-based system, or a simple computer spreadsheet or basic database – such as Microsoft Excel or Access – would suffice, provided that source documents and hard copies of the computer records are retained.

#### 4.6 STAFF AND TRAINING

It is necessary to have a suitably experienced individual who is resident within the EU and who has been notified to the regulatory authorities as Qualified Person for Pharmacovigilance for Europe. If not medically qualified, the QP must have access to a physician and there must also be appropriate arrangements for deputising. Copies of the regulatory notification letters should be available.



Processes for contacting the QP and deputy out-of-hours need to be in place. The regulatory considerations relating to the EU QP have been reviewed by Brown.<sup>11</sup>

It is difficult to provide guidance on what constitutes adequate levels of staffing for pharmacovigilance, but an insufficiency will probably be apparent from the unsatisfactory quality of pharmacovigilance work that has been achieved. It is also necessary that experience and expertise are matched to the tasks being carried out. For those aspects of the work requiring an understanding of disease and medical procedures, some clinical background would be appropriate – for example nursing, clinical pharmacy. In Europe at least, there is no requirement for a company to employ a physician, but for more complex medical issues, either medical training, or access to someone with this is needed. As an example, medical knowledge is needed in determining whether or not an adverse event is medically important (and hence serious). Similarly, this would be needed for evaluating causality in a complicated case.

In the United States, the Proposed Rule incorporates a requirement that licensed physician(s) at a company must be responsible for “content and medical interpretation” of data/information submitted in post-marketing reports (including PSURs)<sup>10</sup> – again, this is a proposal, but the intent is clear.

Suitable training programmes should be available to staff – including training on company SOPs and in pharmacovigilance/clinical safety at a level commensurate with the expertise required according to the employees’ job descriptions and applicable procedural documents. As with all activities, there is a need to be able to demonstrate to the inspector that this has been effectively carried out. Therefore, training records for each employee (including staff working under contract) must be maintained. These should include dates and locations of training sessions (both in-house and external, such as health professional association meetings or other specialised conferences) that have been attended; brief descriptions of the training – ideally with reference to training materials that have been retained centrally; and certification of attendance and/or proficiency, signed by the trainer.

It is vital that training on SOPs and relevant regulations is not limited to pharmacovigilance staff, but extends to everyone working for the company that might, at some time, need to receive or handle an adverse event report. This should include all sales and marketing staff; compliance/quality staff; administrative, security and secretarial staff; medical information personnel; regulatory affairs, medical services and clinical research staff. Senior corporate management should not be exempt from the process.

## 4.7 RECEIVING AND HANDLING ADVERSE EVENTS

Robust processes, supported by appropriate SOPs and quality control, must be in place for the receipt of adverse events and their subsequent handling. This requires that the procedures for receipt of adverse events must extend to subsidiary as well as headquarter offices and to other organisations with which the company concerned has a relationship – such as co-marketing and licensing partners and contract research organisations. Arrangements must be formalised and defined between headquarter and subsidiary offices and the respective responsibilities for receiving, recording and communicating reports of adverse events specified.

All possible sources of adverse events must be covered worldwide. These include reports received by any employees or those working for the company under contract, and extend to spontaneous reports, those “disguised” as requests for medical information, clinical trial adverse events, adverse events constituting litigation proceedings, reports from the company website, published scientific literature and reports from the media.

There is a need for specific procedures describing screening of the worldwide scientific literature for relevant publications on safety related to active substance of the company’s products. This should cover articles published in “indexed” journals – *i.e.* those that appear in searches with, for example, Embase or Medline – as well as those that appear in local medical and associated publications that are not included in literature databases.

Each step in the process from first receipt of a report of an adverse event by anyone working for the company needs to be documented in an SOP and the activity recorded and tracked. This includes:

- Date of initial receipt, by whom and how received
- Internal transmission to the appropriate pharmacovigilance personnel
- Entry on database
- Evaluation for seriousness, expectedness, causal association, impact on benefit–risk
- Expedited reporting, including decision-making for this, where submitted, when and how
- Case closure, filing and archiving
- Procedures for follow-up, with reiteration of the above processes

Exchange of safety information with licensing and marketing partners (“third parties”) must be subject to written agreements – how adverse event reports are handled, who is responsible for entry on the database, for expedited reporting, literature review, responses to regulatory agency/other governmental inquiries, *etc.*

There need to be documented arrangements between the pharmacovigilance and product complaint/product quality departments so that safety issues arising from product defects can be handled appropriately, and *vice versa* (*i.e.*, maintaining an appropriate index of suspicion for possible product problems when receiving and evaluating AE reports).

In addition to these processes for adverse events, there must be documented procedures for informing the pharmacovigilance department about possible new risks on marketed products that may be identified from toxicology and other non-clinical studies and from clinical trials and pharmacoepidemiology studies. There are likely to be obligations for reporting these findings to regulatory authorities, if benefit–risk evaluation for a product may have changed as a result of these findings.

## 4.8 PERIODIC REPORTING

Much attention is paid to PSURs in the CPMP Position Paper on Pharmacovigilance Compliance.<sup>8</sup> Several aspects of these may be open to inspection. In addition to confirming that the PSUR format is appropriate, inspectors examine the contents of the PSUR for completeness and accuracy and may check whether individual cases have been reported appropriately to the respective authorities.

Thus, there needs to be a documented process for the preparation of PSURs, with suitable procedures for review of the documents and for quality control. Careful attention needs to be paid to the format of the PSUR, which should accord with the guidance provided by ICH E2C and the corresponding addendum. Each of the sections described in the ICH guidelines needs to be present in the PSURs.

It is important that there is a timetable for PSUR preparation and submission and that this relates to the respective product birth-dates. A log or database tracking the submission of completed PSURs to the appropriate regulatory authorities needs to be maintained and review of this at intervals by the European QP should be undertaken and recorded. There must be a mechanism in place for describing in the PSUR, or in a separately submitted covering letter, any differences between the Company Core Safety Information and the national Summaries of Product Characteristics.

While US TPSRs are not nearly as comprehensive as PSURs, and do not entail the same level of preparation and evaluation, they too are subject to regulatory scrutiny during inspections, and there are significant penalties for inappropriate reporting of new expedited cases in a periodic report.

## 4.9 ONGOING SAFETY MONITORING

There are regulatory requirements for monitoring the safety of marketed medicines. Volume 9 refers to “ongoing pharmacovigilance evaluation during the post-authorisation period”. However, it is not apparent from regulation or guidelines as to what exactly may be required to satisfy inspectors. The general understanding is that the company must have in place processes for evaluating individual case reports, looking for trends in reporting and for reviewing cumulative reports and events. A method for detecting possible signals is needed and there should be procedures for evaluating these and for making decisions about any action that is required. In particular, the regulations require that possible changes to the benefit–risk evaluation of a product must be notified to regulatory authorities, so there needs to be a mechanism that ensures that this will happen.

Many companies have a safety committee that reviews possible signals and decides upon, or recommends to top management, a course of action in each case. Minutes from meetings of such a committee should be maintained and it has been known for European inspectors to demand sight of these – including when the committee is constituted in the United States.

European inspectors are also interested in the processes whereby an urgent safety restriction could be put into effect for a product, so again it is necessary that there is a mechanism for this and appropriate documentation in support.

In the United States, the same emphasis on ongoing monitoring of a product’s evolving benefit–risk profile is demonstrated by FDA safety-related initiatives, regulatory changes and new guidance documents over the past several years. That this philosophy underpins the Proposed Rule is manifested by such revisions as specifying that it is not only individual serious, unexpected ADEs/AEs that require expedited reporting, but any information sufficient to consider changes in a product’s administration, based on appropriate medical judgement. Such information would include significant unexpected *in vitro*, animal or human (clinical; epidemiological) study safety findings or aggregate data from studies suggesting significant risk to humans (*e.g.*, mutagenicity, teratogenicity or carcinogenicity).<sup>10</sup>

## 4.10 RESPONDING TO REGULATORY ENQUIRIES ABOUT SAFETY

There need to be documented procedures for responding to enquiries from regulatory authorities whenever these may arise. Indeed, the availability of appropriate staff to handle urgent safety issues at any time must be assured, with appropriate processes in place for suitable out-of-hours cover.

## 4.11 QUALITY SYSTEMS

In order to ensure that processes are in place for all aspects of pharmacovigilance and clinical safety monitoring, it is necessary to have a comprehensive system of company policies, SOPs and, if needed, working practice documents. These entities need to cover all the activities involved and assign roles and responsibilities to specified jobholders with associated time-lines. It is usual for these documents to be generated in accordance with an over-arching SOP and for their production, review and distribution to be controlled. Activities and processes that need to be covered (as delineated by EMEA, but also generally applicable to the US)<sup>9</sup> by suitable SOPs or similar documents are shown in Table 1. It is necessary to have comprehensive coverage of the company’s pharmacovigilance operation worldwide, through an inter-related scheme of global, regional and local SOPs.

An essential element of the quality system is training of staff on the content of the various documents, the performance of the training in turn being recorded. Individuals also need to be trained in the scientific and regulatory aspects of pharmacovigilance to a level sufficient for them to understand their work and the part that they play.



**Table 1** *Processes that must be covered by SOPs (EMA)<sup>9</sup>*

- 
- The activities of the Qualified Person
  - The collection, processing (including data entry and data management), QC, coding, classification, medical review of individual case reports
  - Reports of different origin should be addressed:
    - EEA and third countries
    - Healthcare professionals
    - Sales and marketing and other personnel
    - Licensing partners
    - Regulatory authorities
    - Literature
    - Clinical trials
    - Compassionate use
    - Patients
    - Other
  - Follow-up of these reports
  - Detection of duplicate reports
  - Expedited and electronic reporting of individual case safety reports
  - Preparation, processing, QC, review and reporting of PSURs
  - Continuous monitoring of the safety profile of authorised products
    - Notifying authorities and healthcare professionals of changes to risk benefit balance
    - Signal generation and review
  - Risk-benefit assessment
  - Responses to requests for information from Regulatory authorities
  - Database or other record system
  - Handling of urgent safety restrictions and safety variations
  - Meeting CHMP commitments for centralised marketing authorisation
  - Risk Management System and Pharmacovigilance plans
  - Internal audit of the pharmacovigilance system
  - Staff Training
- 

Checking of documents relating to individual adverse event reports and to aggregate data is necessary to help ensure that consistency and accuracy are maintained. Such quality control processes need to be built into the various pharmacovigilance activities.

Satisfactory performance of the system and the processes should be tested by routine internal audit against the SOPs. Generation and review of metrics that quantitatively define the level of performance is also useful.

#### **4.12 STANDARD OPERATING PROCEDURES**

In the United States, under CFR 314.80, 310.305 and 600.80 (and applicable under 314.98), any person subject to post-marketing ADE/AE reporting requirements must develop “written procedures” for “surveillance, receipt, evaluation, and reporting” of post-marketing ADEs/AEs to FDA.<sup>6</sup> The enforcement guidance for inspectors provides recommendations for determining

adequacy of SOPs for ensuring “that ADEs are properly evaluated and are reported to the agency as required by regulations” – these include a designated office with final authority/responsibility for performing ADE regulation-mandated duties and description of how ADE reports are tracked, investigated and evaluated. The list is specifically denoted as not being all-inclusive.<sup>7</sup>

In the EU, guidance exists on SOPs that are considered essential<sup>9</sup> as shown in Table 1. However, there are other elements that are not covered which appear to be equally important. Thus, we consider that the following SOPs should also be available:

- Writing, approving, maintaining, version control of SOPs
- Receipt and follow-up on pregnancy, abuse, misuse reports
- Database searches
- Handling product problems and associated AEs
- Routine screening of scientific literature
- Third party arrangements, licensing, co-marketing, standard statements in agreements
- Safety monitoring in clinical trials, standard statements for clinical trial protocols
- Record retention and archiving

Thus, companies must generate safety-related processes and SOPs that will fulfil both regulatory and corporate requirements despite generally sub-optimal guidance from regulatory agencies worldwide, and no international consensus as to what constitutes a model SOP – in that regard, Goldman has drafted lessons learned from auditing safety-related processes and procedures internationally.<sup>12</sup>

#### **4.13 THE ROLE OF THE QUALIFIED PERSON IN PHARMACOVIGILANCE FOR EUROPE**

The appointment of the Qualified Person for Pharmacovigilance (QP) for Europe and of a deputy (if appropriate) should have been notified to the respective regulatory authorities and a copy of the notification should be available for review by the inspectors. The responsibilities of the QP are laid out in European legislation and in Volume 9, and guidance on the implementation of the role has been issued by the European Federation of Pharmaceutical Industry Associations (EFPIA). Brown<sup>11</sup> described the structures and activities that are required for the QP to fulfil the regulatory obligations, in the context of the company’s quality processes.

For the purposes of an inspection, the key elements are that the QP should be aware of the pharmacovigilance systems that are in place, know what is happening with regard to the safety of the company’s products and be capable of influencing decisions about product safety. To this end, the QP needs to be able to demonstrate that he/she has access to the safety database, can identify products that have marketing authorisation in the EU and is informed about safety findings on products that are authorised or for which marketing authorisation has been sought.

#### **4.14 PREPARATION FOR THE PROCESS OF INSPECTION**

The long-term advanced preparation comprises establishing quality systems as described above. Testing the systems by routine audit – either by company quality assurance staff who are familiar with the particular requirements of pharmacovigilance or by external auditors – is of course needed, and may be thought of as one element of long-term preparation.

Training is a vital element of assuring and maintaining quality. However, one aspect that is of particular value is to train all potentially involved staff in what they need to do in the inspection itself. This may be achieved as part of the routine auditing by offering feedback on how individuals performed, for example, when interviewed by the auditors. Aspects of the desired behaviours are

presented in Table 2. If this training has not been provided previously, it may usefully be given in any time that is available following notice that an inspection is going to occur.

One other activity may assist in the advanced preparation for EU inspection, (and US inspection as a useful exercise, not regulatory requirement), as well as being of help to company or external auditors and to new pharmacovigilance staff. This is the drawing up and routine updating of an overview of the pharmacovigilance operation throughout the company. The UK MHRA requires companies under notice of inspection to complete a document referred to as the “Summary of Pharmacovigilance Systems”.<sup>13</sup> The document includes a requirement for the company to submit contact details and various summaries; lists of products and marketing authorisations; outline of the company structure and the operating model for pharmacovigilance; a summary of the pharmacovigilance activities undertaken in the UK; details of current and previous computer systems; the quality management system; training record system; and archiving. In addition, detailed information is required, including: organograms for pharmacovigilance and medical information; CV and job description for the EU QP; details of all products authorised in the UK; details of all studies ongoing in the EU and post-authorisation studies globally; lists of SOPs and associated documents; compliance metrics for expedited and periodic reports; details of third-party agreements and outsourced pharmacovigilance activities; and information on recent product-related safety issues.

The MHRA additionally requires prior submission to the inspection team of various documents, including SOPs on the following: case processing of spontaneous ADR and clinical trial serious AE reports; case follow-up; expedited reporting and monitoring of compliance with this; PSUR preparation and submission; signal detection and trend analysis; and medical information handling of enquiries.

The preparation of this documentation is time-intensive and the need to provide it to UK inspectors at relatively short notice (this may be 6 weeks or less) can be problematic at a time when much else may need to be done.

Another item that may be considered well in advance of any inspection is whether there are items that might not be readily provided to the inspector without discussion. Thus, for example, there may be sensitive financial information within third-party agreements that is not relevant to a

**Table 2** *Aspects of the desired behaviours*

<i>Inspector</i>	<i>Employee</i>
Requests sight of document	Knows location, provides all appropriate materials
Requests sight of document that is not available	States that document is not available, or that time is needed to provide it
Asks question	Provides answer to the question, limits response to answering the question asked
Asks unclear question	Requests clarification
Asks inappropriate/contentious question (as previously defined – see text)	Asks for permission to refer to superior before giving response
Asks question to which the answer is not known	Admits ignorance, or admits uncertainty about the response, preferably stating how the correct answer may be obtained by reference to other staff or to a document
	Does not argue with the inspector or express impatience
	Is seen to cooperate fully
	Does not volunteer information
	Does not imply criticism of company, colleagues or others

pharmacovigilance inspection. It might be decided to prepare extracts from the contracts that can be made available to the inspectors instead of giving the full document, informing the inspectors accordingly.

Findings from internal audits fall within this category. It may be reasonably argued that showing full audit reports to regulatory inspectors may lead to guardedness in reporting negative findings from audits that in turn would compromise quality. Hence, the company position could be determined in advance of an inspection as to whether audit reports would be provided willingly, only if insisted upon after due explanation of the company's serious concerns, or whether, for example, executive summaries could be offered as an alternative to the full reports. Needless to say, reluctance to provide the full report might be interpreted by the inspectors as meaning that the company has something to hide. In a similar vein, if a company has uncovered deficiencies through a voluntary audit and taken appropriate remedial action, such manifest quality assurance/quality control efforts may well demonstrate to a regulatory inspector that the company has performed due diligence in a good faith effort to comply. Thus, when the inspector finds the same past deficiencies that have been addressed, it is certainly a more favourable situation than if the deficiencies have gone undetected and unattended.

In the immediate run-up to an anticipated inspection, it is vital that the following are in place:

- Top management are aware of the imminent inspection and a process for high-level daily feedback of important findings agreed.
- If an affiliate office is being inspected, that the appropriate headquarters departments are informed.
- All heads of departments whose staff might be interviewed or whose processes or documents could be inspected are aware of the occurrence and understand the need for full cooperation and of the importance of the event. This includes personnel in charge of security and reception staff, as well as those responsible for training, sales and marketing, quality assurance/product complaint evaluation, regulatory affairs, clinical research, medical affairs, medical information, archiving, legal, *etc.*
- All staff involved in activities that could bring them in contact with inspectors should be briefed on how to behave towards the inspecting team and on the priority that should be given to responding to the requirements of the inspectors.
- Offices and other areas that may be seen by the inspectors should be checked for the presence of extraneous or sensitive material that may be on display.
- Documents that have been requested by the inspectors need to be made available and have been checked for completeness. In particular, ensuring that job descriptions, CVs and training files are up to date and complete.
- Adequate facilities are available for the inspection team.
- Staff are assigned to accompany the inspection team, to ensure that they have access to required documents or personnel, and to record what documents have been provided to the inspectors.

#### **4.15 REMEDIATION FOLLOWING INSPECTION**

It is essential that all who are responsible for pharmacovigilance activities are involved in reviewing and providing comments on initial reports from the inspectors. The latter may be reasonably challenged on factual errors in their findings. It is a matter for high-level discussion within the company as to whether they might be challenged also on interpretation of the regulations, but in general this probably does not happen.

A careful and adequate response to the inspection findings must be prepared, including realistic commitments that the company is prepared to make regarding remedying failures in compliance. The remedial action plan must include detailed steps and time-lines that are achievable. It is

essential that top management in the company are involved at an early stage in any aspect in the commitments that may involve a need for additional resources, whether employed or out-sourced.

When there are extensive adverse findings, it may be necessary to set up a task force in the company to respond to these and to oversee the implementation of the action plan. Top management support may be needed if the necessary priority is to be given to these activities.

#### 4.16 CONCLUSIONS

The likelihood of regulatory inspections of pharmacovigilance practices and systems should be seen as providing a stimulus to the company to ensure that its house is in order. This requires a long-term and continuing commitment to quality within the company. The options for preparation when an inspection is imminent are limited.

In our view, the objective of the exercise should be seen – and be presented as such – in wider terms. It is not a matter of ensuring compliance with regulations. Rather, compliance should be viewed as a necessary step in ensuring that the company fulfils its wider obligations for monitoring the safety of its products, guarding its assets and – above all – protecting patients from unwarranted or avoidable risk.

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## CHAPTER 5

# Investigator, Sponsor and Contract Research Organisation Audits

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## 5.1 INTRODUCTION

The conduct of medical research in human subjects is guided by the principles set out in the Declaration of Helsinki (WMA, October 2000). The declaration is a statement of the ethical principles to which physicians and others associated with medical research should adhere. The internationally accepted quality standard of Good Clinical Practice (GCP) was developed to ensure that researchers applied the appropriate ethical and scientific standards in the design, conduct, recording and reporting of medical research. In 1997 the Committee for Proprietary Medicinal Products (CPMP) published a detailed guideline, produced by the International Conference on Harmonisation (ICH), on the implementation of GCP in clinical trials on human subjects (GCP CPMP/ICH/135/95). The application of GCP as the quality standard for clinical research in Europe became a law in April 2001 with the introduction of directive 2001/20/EC, and is the standard to which all sponsors of clinical research must adhere for submission of data to European regulatory authorities.

As with other quality standards, ICH GCP requires that a system of Quality Assurance (QA) and quality control (QC) is implemented within organisations conducting clinical research. The auditing process is an integral part of this quality system, and provides a “snap-shot” of the standard to which clinical research is being conducted.

There has been minimal guidance for sponsors from the regulators on the extent of auditing that should be carried out. ICH GCP considers it to be the sponsor’s responsibility to decide on how to audit, the frequency of audit, the type of audit and the form and content of audit reports (ICH GCP Section 5.19.3). It is neither necessary, nor feasible, to audit all clinical studies within a development programme. The number and type of audits to be conducted during a compound’s development, should be built into the development plan.

This chapter deals with the methodology for the conduct of Investigator Site, Sponsor and Contract Research Organisation (CRO) audits. There is no formal guideline approved by the regulators for the conduct of these audits. However, the European network of GCP Auditors and other GCP Experts (ENGAGE) has produced an optional guideline for GCP compliance and quality systems auditing (21 August 1997) based on the requirements of ICH GCP. Data audits are discussed in Chapter 6 while GLP ‘site audits/inspections’ are discussed in Chapter 17.



## 5.2 INVESTIGATOR SITE AUDITS

The development programme for a new active substance (NAS) should identify which clinical studies will be audited. Each organisation should have its own criteria to select studies for audit. Studies should be audited at each phase of development (Phases I–IV) (see Chapter 10). The criteria for selection for Phase I–IV studies would probably include:

- key dose-finding studies;
- key decision-point studies;
- key safety and efficacy studies;
- pivotal registration studies.

Clinical study audits are also carried out on Phase IV studies, particularly large outcome studies where several hundred centres and several thousand patients are involved. Audits on these mega-trials are often approached from a systems audit (Section 5.3, Sponsor Audits) perspective to maximise the use of available resources.

In this section the audit process will be described for routine audits of multi-centre Phase II and III studies.

### 5.2.1 Planning and Preparation

**5.2.1.1 The Audit Plan.** The starting point for conducting any audit is the Audit Plan, which provides an overview of the activities and timelines for the audit. The Clinical Study Team should supply the auditor with all necessary documents to prepare the Audit Plan, such as the protocol and any amendments, case report form, details of participating sites, recruitment figures and reported Serious Adverse Events (SAEs). The contents of the Audit Plan might include

- brief details of the study to be audited;
- objectives of the audits;
- scope of the audits;
- approximate timelines for the preparation, conduct and reporting of the audits;
- site-selection criteria to be used;
- outline of tasks that will be conducted during each site audit;
- location of Essential Documents;
- auditing standards (SOPs to be used and regulatory documents to be referred to);
- reporting procedure;
- responsible auditor(s) and contact details;
- contact details for relevant Clinical Study Team members including CRO contacts if applicable.

The Audit Plan should be shared with the Clinical Study Team (and monitors if sites have been identified for audit) to ensure that they are all informed of what will be done, when and where. The Audit Plan is usually signed by the auditor and QA Management, and/or a member of the Clinical Team. The authorisation process varies between companies.

**5.2.1.2 Timing of Investigator Site Audits.** The investigator site audits can be initiated at any time, but usually occur after the study has started (*i.e.*, post-site initiation), depending on the requirements of the Clinical Study Team. Audits conducted shortly after sites have been initiated would provide useful information on the set-up of the study, suitability and readiness of the study team and consistency of documents across sites.

The objective of an audit conducted early in the study is to identify quality issues and correct them at an early stage. However, more information can be obtained about the quality of a clinical study by auditing sites during the recruitment and treatment phases of the study. Each study should be assessed to determine what the optimum auditing timelines would be to maximise the benefit to the Clinical Study Team. Conducting audits at a late stage during the study, or even after study completion, limits the benefit of the audit findings, as it might be too late to implement all of the necessary corrective actions to improve the overall quality of the study.

**5.2.1.3 Site Selection.** Following initiation of the study, the auditors should ensure that they receive regular updates of the recruitment status of each site. This information is important in selecting sites for audit and planning the audit schedule. Various criteria are used for site selection, these might include:

- rate of recruitment;
- number of subjects recruited;
- experience of investigator;
- number of SAEs reported;
- monitor's concerns;
- concerns with the CRO;
- level of involvement of investigator in company's studies;
- request of the Clinical Study Team;
- geographical location.

The number of sites to be selected for audit in a multi-centre study will depend on the available auditing resources, the time frame for completion of the audits and the appropriateness for the study. Organisations sometimes use sampling tools, which are commonly used for quality-control testing of manufacturing batches, such as BS6001. Alternatively, an arbitrary percentage might be used such as 20%, or a fixed number of sites, for example 3, might be selected irrespective of the size of the study. There are no guidelines on the sample size to use, but it should be of sufficient size to obtain information on systematic issues affecting the study, and to assess the consistency in the implementation of the protocol in different regions (particularly in a multi-national study). The effectiveness of the monitor (Chapter 9) is critical to the quality of data generated in specific sites. Therefore, it is recommended that sites monitored by different individuals are selected for audit.

**5.2.1.4 Notification of Audit.** It is recommended that the sites are contacted as soon as they have been selected to schedule the audit. Most organisations prefer the auditor to liaise with the site monitor, who is also invited to attend the audit, to arrange the audit dates with the investigator. A minimum notice period of 2 weeks should be allowed, but it can take a month or more before the audit actually takes place owing to absence of the investigator, monitor or key members of the study team.

Once a mutually convenient date for the audit has been agreed, the auditor should confirm this with the investigator in writing. The letter should provide details of the purpose of the audit, what will be audited and by whom. A list of contents, which might be included in the letter, is given below:

- title and protocol number of the study to be audited;
- date(s) and times the audit will start and finish;
- documents, facilities and equipment the auditor will need access to;
- study team members the auditor would like to interview (*e.g.* Investigator, Study Nurse, Pharmacist);
- approximate timing and duration of interviews;
- facilities for the auditor to review documents and conduct interviews.

In many cases, the investigators will not have been audited before, and it is therefore useful to provide them with further background information about site audits. The ABPI and BARQA (see Glossary) produce useful pamphlets for investigators about the audit process, which can be sent with the notification letter. It is advised that copies of all correspondence with the investigator be provided to the Clinical Study Team and respective monitors, to ensure that they are aware of the information being given to the investigators. Maintaining optimum communication levels with all involved parties is very important to ensure that the audit proceeds without problems.

**5.2.1.5 Worksheets.** Auditors often use worksheets to facilitate the audit process. These documents are usually used as a guide to ensure that all of the necessary auditing tasks are carried out, and that the audits are conducted consistently between sites. The use and design of worksheets varies between organisations and between individual auditors. Worksheets might be very detailed and span more than 20 pages, others might be brief and only a few pages long. The type of worksheet used depends on the policy of the organisation and also on the individual working practices of the auditor. Several worksheets might be used for an investigator site audit. Examples of worksheets are listed below:

- Investigator/study team interview worksheet
- Essential Documents worksheet (based on ICH GCP §8)
- Patient information leaflet worksheet (to check ICH GCP compliance)
- Informed consent worksheet (to check timing of consent prior to screening)
- Investigational product (IP) storage, dispensing and accounting worksheet
- Source data verification (SDV) worksheet
- Facility worksheet (including Pharmacy and Laboratory as well as specific patient tests, *e.g.* ECGs).

The worksheets can be set-up electronically and completed on site. This is not usual for the study team interviews however! Using an electronic tool for auditing can facilitate data basing of audit observations and subsequent trending analysis.

## **5.2.2 Conduct of the Audit**

**5.2.2.1 Essential Document Review.** The audit of an investigator site is usually conducted in two parts. Firstly, an audit is normally carried out on the original copies of the Essential Documents held in the Trial Master File set-up by the sponsor organisation (or delegated CRO). This is then followed by the audit at the investigator site.

Essential Documents are defined by ICH GCP §8 as “those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced”. The relevant SOPs for the collection, review and filing of Essential Documents should be provided to the auditor by the Clinical Study Team to facilitate the audit.

The document review should preferably take place within a couple of days of the planned investigator site audit. During the review the auditor should document version numbers, document dates and approval dates for subsequent comparison with the Essential Documents held by the investigator.

Translations might be required for some documents such as Independent Ethics Committee (IEC) approvals and patient information leaflets. Any translations should be signed and dated by the translator and either certified as accurate by an independent translator, or verified by independent back-translation.

Monitoring reports should be carefully reviewed to obtain an insight into issues occurring on site and to assess the level of monitoring. The frequency and extent of monitoring activities should be

compared with the Monitoring Plan for the study (if available) or SOPs. Actions taken to issues raised by the monitor should be followed through to completion. To this end, monitoring SOPs should contain the review and approval process for monitoring reports.

In addition to conducting an audit on the Essential Documents, a review of the facilities usually takes place. The storage conditions for the Trial Master Files and completed Case Report Forms (CRFs) should be checked for security, and if the company holds investigational products prior to distributing to the sites, these storage areas should also be checked.

Following the review of the Essential Documents and review of the storage facilities, a close-out meeting should be held with the appropriate members of the Clinical Study Team and/or relevant monitor(s) to provide feedback on the audit observations. Any documents, which should have been on file but were not found, should be requested from the Clinical Study Team before completing the audit. The audit reporting procedure, and the team's responsibilities with regard to following-up audit observations, should be discussed at the close-out meeting.

**5.2.2.2 Site Audit.** It is a good practice to ask the site monitor to be present at the audit. There is no reason why the audit should not be scheduled with a routine monitoring visit, which would minimise the disruption to both the monitor and site. The monitor can provide support to the investigator and help the audit to proceed smoothly and efficiently. Monitors can provide a valuable resource to auditors in helping to locate documents, act as an interpreter (if necessary) and provide information about medical practices in their country.

**5.2.2.2.1 Opening Meeting.** An investigator site audit should always start with an opening meeting with the investigational team, the purpose of which is to:

- Introduce the auditor to the investigator and study team
- Outline the scope and objectives of the audit
- Discuss the agenda for the audit, arrange interview times and schedule the close-out meeting
- Familiarise the auditor with the study documentation, patient medical notes, facilities, equipment and other departments (if applicable)
- Confirm contact numbers for the investigator and study team members during the audit.

**5.2.2.2.2 Investigator and Study Team Interviews.** At an early stage during the audit process, 30–60 min should be allocated to interviewing the investigator and site staff involved with the study. The purpose of the interviews is to establish how the protocol has been implemented, how subjects have been identified and recruited, and what responsibilities have been delegated by the investigator and to whom. The scheduling of the interviews depends on the availability of the investigator and site staff. The auditor should endeavour to schedule audit activities around the normal daily routine of the clinical department, and thus minimise disruption.

The information from the interviews should be substantiated by documentation available in the site study files. Any discrepancies should be clarified with the site staff, or considered as observations.

**5.2.2.2.3 Facility Review.** The investigator, or one of the study team, should be asked to show the auditor around the clinic area so that the facilities used for the study can be reviewed. Examples of some of the areas that should be looked at include:

- Subject visit areas
- Storage facilities for medical records, study documents and investigational products
- Laboratory area (for blood sampling, centrifugation, cold storage, *etc.*)
- Equipment used in the study (if applicable), for example ECG equipment, BP monitors
- Computer room/facilities (see also Chapter 37).

The facilities and equipment should be assessed for appropriateness with the study requirements, acceptable maintenance and calibration logs (where applicable), and general suitability for use in a clinical study.

If patient notes are routinely stored electronically on site, the auditor should check that the computer system being used meets GCP requirements. It should be possible to demonstrate the following functionality for the computer system:

- An audit trail to ensure that any changes made in the system can be tracked
- Virus checker to limit the chance of a computer virus affecting the system and/or data
- Regular back-ups are made and stored securely off-site
- Adequate physical and logical security systems (password protection and different access levels for staff, locked or limited access to where the computer is housed)
- Disaster recovery plan is in place
- Electronic signatures for investigators.

If the system does not fulfil the minimum criteria, then the investigator should be requested to print off the source data at each visit, sign and date the visit and retain the paper copy for SDV. For the screening or first visit this should also include the medical history and other supporting evidence to confirm inclusion and exclusion criteria.

Several national regulations stipulate that the investigational products are under the control/authorisation of a Pharmacy/Pharmacist (Chapter 8). As such in hospital-based studies the investigational product(s) are often stored in the Pharmacy department. If this is the case, an appointment should be arranged to visit the Pharmacy, to review the Pharmacy Study File, check the storage conditions and interview the responsible Pharmacist (if applicable). The auditor should conduct drug accounting on a sample of supplies to check the reliability of the available drug-accounting documentation.

If code envelopes are used, the auditor should determine who retains them – the investigator or pharmacy department. The code envelopes should be checked to ensure that there is an envelope for each set of IP on site and that none of the codes have been opened. If a code has been opened, then this should have been done according to the protocol requirements. The reason for the code-break should be fully documented including the date, time and signature of the person responsible for breaking the code.

**5.2.2.2.4 Essential Documents Review.** The study files on site should contain most of the Essential Documents previously checked in the Trial Master File in-house. The key difference is that the monitoring reports (except for the Initiation Visit Report) will not be present. The site files should contain additional information such as the Subject Identification code List, the Subject Enrolment Log and signed and dated Informed Consent Forms. All of these documents identify the subjects and should not be included in the Trial Master File in-house.

Many of the documents located on-site will be photocopies of originals in the Trial Master Files, except for correspondence with the IEC, which usually takes place directly with the investigator.

**5.2.2.2.5 Source Data Verification (SDV).** A sample of completed CRFs, SAE reports and Consent Forms should be cross-checked against source documents in order to verify that the investigator has conducted the study according to national regulations, ICH GCP, the protocol and any amendments.

The sample size is determined from the number of subjects randomised into the study at the time of audit. An arbitrary statistic that is often applied to calculate the sample size is  $\sqrt{n+1}$ , where  $n$  is the number of subjects recruited. However, the actual extent of SDV that is conducted will also be influenced by the complexity of the study, the amount of data available per subject and the amount of time available to the auditor.

The extent of SDV that is required during an audit should be defined in the SOPs of the QA department. The SOP should specify the method of determining the sample size, how many (if any) CRFs should be verified 100%, what types of parameters should be verified 100% and which parameters can be sampled. For the sample of CRFs selected, it is usual to conduct 100% SDV of inclusion and exclusion criteria, and key efficacy and safety parameters. The Clinical Study Team should be able to advise the auditors on these issues, if they are not apparent from the protocol.

It is common practice to verify all SAE reports occurring at a site against the source data, and to check the timelines of the reporting process against SOPs and regulatory requirements (nationally and internationally, if applicable).

Consent Forms are frequently checked 100%, but for sites with a large number of subjects this might be neither feasible nor necessary if the process appears to be compliant with ICH GCP. The version of the Consent Form used should be checked to ensure that it is the version approved by the IEC. The dated signatures of the subject (or legal representative) and investigator (and witness, if applicable) should be checked to ensure that consent was obtained prior to any protocol-related procedures being conducted. The handwriting on the forms should also be reviewed to ensure that the subjects have signed and dated their own signatures. The name of the person obtaining consent from the subjects should be legible to confirm that they have the authority (their name should be on the site delegation list) to carry out the consent procedure.

**5.2.2.2.6 Close-Out Meeting.** Following completion of all audit activities on site, a close-out meeting should be arranged with the investigator and study team to obtain clarification on any issues and provide details of observations made. Prior to the meeting the auditor should spend approximately 15–30 min preparing for the meeting by summarising all of their observations. The auditor should initially thank the investigator and study team for their co-operation and time during the audit. Feedback on audit findings should be given in a positive and constructive manner where possible to maintain motivation of the study team. The auditor should document the observations reported back to the investigator.

The study team should be informed of the reporting process and advised that they will not receive a copy of the audit report as it is an internal document, but that the monitor will follow up any corrective actions directly with them.

**5.2.2.2.7 Follow-Up.** On returning to the office the auditor should write to the investigator thanking them for their co-operation, and reiterating the reporting procedure.

### 5.2.3 The Audit Report

The audit report should be written as soon after completion of the audit as possible. This would enable the Clinical Study Team and monitor to take corrective action promptly, and it would also ensure that the audit observations were still fresh in the auditor's mind. The past tense should be used for all activities performed, documentation reviewed and observations made. The content and format of audit reports varies enormously between organisations. Some companies prefer brief reports (less than 4 pages) that state issues rather than observations and ignore minor discrepancies. Other organisations want to receive highly detailed reports which document all audit activities and observations made. In order to decide on the format and content of audit reports it is useful to ask for the recipients' input into the design. Alternatively, provide clinical management with some examples of reports and ask them to comment on the usefulness of the format for their needs.

Audit reports might include the following contents:

- **Front page** – stating the type of audit, study title and protocol number, audit date(s) and location(s).



- **Executive/Management Summary** – this section should provide an overview of the audit and the most important audit observations.
- **Introduction** – a brief summary of the audit, including key details of the conduct of the study at the site.
- **Observations Section** – this section can be sub-divided according to the seriousness of the audit observations. Each observation should be numbered, clearly and unambiguously explained with reference to the protocol section, SOP, guideline or regulation concerned. Many organisations require the auditors to make recommendations for corrective actions, but some prefer the clinical teams to decide on what actions should be taken. If recommendations are made, the auditor should try to provide the most feasible and pragmatic solutions.

In some organisations, provision for written responses to the audit observations is given in the report, and in others, a separate action plan is produced by the study team. The audit report should be signed and dated by the author.

The distribution of numbered copies of audit reports should be limited, and photocopying should be prohibited. This is a precaution to ensure that only the personnel involved with the study, or their management, have access to the information within the report. It is also important to control the distribution of copies so that they do not become accidentally filed in the Trial Master Files, where they might be seen by regulatory inspectors/reviewers.

It is useful for senior clinical management to have an overview of the key issues identified during audits, which impact the study as a whole. This can be provided in the form of a report of all of the key observations from the site audits presented at a high-level focusing on systematic problems. The impact of these procedural issues on the quality of the study can then be more easily assessed and corrective action taken at a senior level in a top-down approach.

### 5.3 SPONSOR AUDITS

The sponsor company, in the context of this section, is the manufacturing organisation. ICH GCP (Section 5.2.1) states that “the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor”. This is the case even when the sponsor transfers some or all of the trial-related duties to a CRO. Most manufacturers delegate the conduct of some of their clinical trials to CROs in order to maximise the resources available to complete the development of a compound in the shortest-possible time period. The sponsor therefore has a duty to select a competent CRO to conduct the studies to the highest standards, and to monitor the CRO’s performance. This is dealt with in more detail in the following section. If the sponsor organisation is conducting all trial-related activities, then it must demonstrate to the regulatory bodies that it has QA and QC systems with written SOPs. The internal quality system is required by ICH GCP (Section 5.1.1) “to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)”.

The manufacturer’s quality system should include a programme of independent audits to ensure that the internal quality controls are optimised and would be acceptable to the regulators. These internal audits, known as “systems” or “process” audits, usually assess all trial-related activities, from the development of the protocol to the finalisation of the study report. The types of audits that can be included in an internal audit programme are:

- SOPs for the preparation, QC and finalisation of study-related documents, for example protocol, CRFs, investigator brochures, informed consent and patient information leaflets
- Monitors’ qualifications and training, and monitoring procedures
- Qualifications and training of other clinical personnel
- Reporting and databasing of SAEs

- Ordering and distribution of IPs
- Data Management procedures
- Statistics procedures (Chapter 32)
- Selection and outsourcing of trial-related activities
- Validation status of computerised systems (Chapter 37).

Any process within clinical development can be subjected to a systems audit. It is recommended that systems audits of functions critical to the success of regulatory submissions are performed on a regular basis, for example, bi-annually as part of the organisation's internal quality system. Although there is an endless possibility for the type of systems audits that can take place, the QA department should have an SOP dealing with the conduct of systems audits and describing the overall approach that should be taken. For each identified systems audit, it is recommended that either a specific SOP, or a section in a single SOP be written, to guide the auditors and system owners through the process. The SOP should then be referenced for the next scheduled audit of the system, which might be conducted by a different team of auditors, thereby promoting consistency.

Systems audits have the advantage that they provide management with an insight into the quality of their clinical development processes across all therapeutic areas, and can help to identify deficiencies. These audits can be conducted across functions, therapeutic areas, departments, countries, *etc.* and thus provide useful information on the consistency of procedures and implementation of regional/global SOPs. By addressing the weaknesses in internal processes, the quality improvements made will have an affect on the quality of all studies and not only those subjected to audit. For organisations with limited QA resources, the conduct of internal systems audits is a more cost and time-efficient utilisation of auditors.

The distinguished quality guru, W Edwards Deming stated that, "Quality is not improved by after the fact inspection, but by control of the production processes as it happens". Deming was discussing the need to introduce quality systems into manufacturing production processes. Another leader in the field of quality, Joseph M Juran, said "85% of common outcome problems can be addressed by changing systems". That is, the quality of the end products can be greatly improved if efficient production systems are in place. The same philosophy applies to any production process, which would include clinical development, where the end product may be a locked database, a clinical study report or a registration dossier.

### 5.3.1 Planning and Preparation for Systems Audits

**5.3.1.1 Notification.** The first task in preparing for a systems audit is to identify all personnel responsible for the system being audited, and notify them formally in writing of the audit and the proposed timelines. It is also usual to notify Senior Clinical Management that an audit of an internal system will be conducted and that they will receive a report of the observations. Systems audits can often be quite complex and involve many different departments. Therefore a high degree of transparency of the roles and responsibilities of the people involved, and regular and efficient communication are the keys to a successful audit.

**5.3.1.2 The Audit Plan.** When the system or systems to be audited has/have been identified a comprehensive Audit Plan should be written. The scope of the audit should be specific and closely adhered to during the course of the audit. Any change of the audit scope should be documented in an amendment to the Audit Plan. All processes in clinical development overlap with one another, making it very easy for "scope creep". The problem with this is that the audit loses focus and becomes very complex to conduct and report.



The Audit Plan should include:

- Brief details of the system to be audited
- Objectives of the audit
- Scope of the audit
- Approximate timelines for the preparation, conduct and reporting of the audit
- Auditing standards (SOPs to be used and regulatory documents to be referred to)
- Reporting procedure
- Responsible auditor(s) and contact details
- Contact details for relevant system owners.

The Audit Plan should be shared with the system owners and Senior Clinical Management to ensure that they are all informed of what will be done, when and where. The system owners should be invited to comment on the scope of the audit, as they would have more insight into the system and the key areas to focus on. If possible, a meeting should be arranged with the system owners and clinical management to discuss and agree the final Audit Plan.

The Audit Plan should be signed off by the auditor and also by the system owner before commencing with the audit.

**5.3.1.3 Documentation.** The background documentation that is required to prepare for the audit should be requested from the system owners. The documentation might include:

- Relevant SOPs
- Staff job descriptions, CVs and training records
- Details of studies that might be involved (with protocols, *etc.*)
- Documentation relevant to the system being audited.

The documentation should be reviewed to gain an insight into the system and the processes involved and to develop worksheets to facilitate the audit process.

#### **5.3.1.4 Conduct**

**5.3.1.4.1 Pre-Audit Meeting.** A start-up meeting involving the system owners and any other staff that might be involved with the audit should be held. The Audit Plan should be discussed and an overview of the audit process with timelines/agenda should be presented. The auditors should be flexible enough to modify the audit agenda if it conflicts with the availability of certain staff or access to specific facilities or documentation.

It should be stressed during the meeting that the focus on the audit is on the system and not on individuals.

Where possible, and if appropriate to the system being audited, meetings should be held with the auditees at the end of each audit day to discuss observations and to ask for clarification on any issues arising from the audit. This helps any misunderstandings by the auditor to be resolved quickly and allows any missing information to be obtained in time for the next audit day, thus helping the process to be more efficient.

**5.3.1.4.2 SOP Review.** The starting point in the evaluation of any system is the review of existing SOPs. These should be critically assessed in terms of compliance with applicable regulations and guidelines, clarity, comprehensiveness, and against the SOP on SOPs to ensure that the SOP is in date and the format and content are correct.

The review of the SOPs should allow initial mapping of the system, and the identification of gaps or areas of non-compliance with current regulatory requirements.

**5.3.1.4.3 Documentation Review.** The documents, which are relevant to the system, should be reviewed for compliance with SOPs to identify any non-compliance issues or deficiencies in the system. For example, to confirm compliance of staff with the SAE reporting system, a sample of SAE reports would be selected from several different projects (to assess consistency between projects). The documents provided to the auditor should include, but may not be limited to:

- the SAE reports;
- fax transmittal forms (if used) from the investigator sites and CROs (if acting as an intermediary) verifying the dates when the forms were submitted to the sponsor company;
- all correspondence relating to the SAE reports;
- narratives produced by pharmacovigilance (if applicable);
- submission reports to regulatory authorities (if applicable);
- coding dictionary used;
- print-outs from the SAE database and the clinical databases (for the individual studies);
- QC documentation.

Depending on the objectives of the systems audit the documents might be reviewed to assess some or all of the following:

- compliance with SOP requirements
- compliance with regulatory requirements, for example reporting timelines from the site to the CRO/sponsor, sponsor reporting times to regulatory authorities;
- accuracy of information provided and transcribed into the databases;
- correct use of coding dictionary;
- cross-correlation between entries in the SAE and clinical study databases;
- timelines from SAE receipt and database entry;
- timeliness and handling of follow-up information on SAEs and updating of databases;
- accuracy of narratives and correlation of severity and relatedness with investigator's assessment;

Meetings with key personnel should be scheduled to coincide with the part of the system being audited at the time. The level of understanding of an individual's role, and their knowledge of the systems' SOPs can be ascertained during the interview process. If there are inconsistencies between the way an individual describes their role and performance of their tasks with what is described in the SOPs, then there is either a problem with the SOPs, that is they do not reflect what is actually done in practice, or the individual requires re-training and closer supervision.

The interviews should be handled sympathetically by the auditor so that the auditees feel at ease and not under pressure. It is usually possible to obtain higher quality information from auditees who feel that they are not under scrutiny, but that the focus of the audit is on the system.

**5.3.1.5 Reporting.** The reporting process should be outlined in the Audit Plan with details of the procedure and timelines. As the report will be used by the system owners as a tool for any process improvements required it should be written in a logical, unambiguous and practical way.

The audit reports are usually submitted to Clinical Management and should be in a format that allows them to quickly understand the key deficiencies of the system, and how the deficiencies might impact on the overall quality of the clinical development process. The report can often be used as a decision tool for Clinical Management with regard to further investment in resources, training or reorganisation.

There are many ways to present information from a systems audit and it is very dependent on the individual organisation's requirements.

An example of the content of an audit report is as follows:

- **Front page** providing information on the system audited, when, where and by whom;
- **Executive summary**, which should be succinct, accurately reflects the outcome of the audit, and clearly identifies any critical or major observations that need immediate management attention. The categorisation of key observations as critical or major should be clearly defined;
- **Contents page**;
- **Glossary of terms**;
- **Background and scope** including objectives of the audit;
- **Procedural observations** categorised according to severity (critical, major, minor, *etc.*) and areas, for example documentation, timelines, database, SOPs;
- Cite which SOPs or regulations were not complied with for each observation where possible (some issues may not be due to non-compliance, but to poor practice);
- **Recommendations for improvements** (this is not always required as some organisations prefer the clinical groups to determine their own course of action).

The auditors should request that the system owners and/or Clinical Management provide responses to each of the audit observations. The responses might be in the form of an action plan, which identifies the root cause of each observation (or groups of observations per area), the actions to be taken and what needs to be done to improve the quality in the future. The action plan should state when the action will be completed and who will be responsible. The preparation of the action plan is a good way to obtain acceptance of the systems owners, and also to provide Clinical Management with evidence that corrective action will be taken.

The action plan might be incorporated into a final report for future reference and follow-up.

**5.3.1.6 Follow-Up.** The action plans produced by the systems' owners should be reviewed by the auditors to ensure that the auditees have understood the observations and have accepted the recommendations (if provided), or decided on appropriate action within acceptable timelines.

The QA department might provide the clinical department with an Audit Certificate specifying that an audit of the system had taken place (including when and where it took place). The Audit Certificates can be used to provide evidence to regulatory inspectors/reviewers of the organisation's internal quality system without providing any confidential information such as the audit reports.

## 5.4 CONTRACT RESEARCH ORGANISATION AUDITS

This section discusses the evaluation of CROs by sponsor companies prior to placing contracts.

Owing to the need for flexible resources in the clinical development process, most pharmaceutical companies outsource many of their clinical activities to CROs. Some organisations operate as virtual pharmaceutical companies and outsource all of their product development to a diverse range of CROs. The rate of growth of the CRO industry is currently running at over 20% per year as a result of the rapidly increasing reliance of pharmaceutical companies on their services.

Although a sponsor might outsource the complete clinical development of its products to a CRO (or multiple CROs), the responsibility for the quality and integrity of the study data always resides with the sponsor (ICH GCP, Section 5.2.1). In addition, the sponsor remains legally liable for the pharmaceutical product and therefore has a duty of care to ensure that it is being properly used by CROs for research and development.

The use of CROs for the conduct of a sponsor's clinical trials is commonplace in clinical R&D, and millions of dollars are spent every year by sponsor companies outsourcing their clinical development programmes. Choosing a CRO that meets the quality standards and expectations of the sponsor is critical to the successful development of a NAS, and can have a significant financial

impact on the manufacturer. If a CRO is selected which does not have the resources or capability to develop the product as required by the sponsor, there could be millions of dollars lost in fees to the CRO, prolonged development time, re-work and delayed registration and marketing. In order to minimise the problems arising with the use of CROs, many of the major manufacturers have a department solely for their selection and management. The day-to-day monitoring of the CROs is usually the responsibility of the Clinical Study Team. The QA department in larger organisations is often utilised in the selection and ongoing assessment of CROs. For virtual pharmaceutical companies this can be the main role of the QA function.

The extent of the evaluation process will depend on the services the CRO will be providing to the sponsor company. The selection and evaluation of a CRO is frequently performed by representatives of the Clinical Study Team and contracts group, but many companies require a more rigorous due diligence audit by the QA department prior to placing a contract.

Common procedures for the conduct of pre-contract audits of CROs can be used whether the audit is of a full-service provider (*i.e.*, a company offering a “one-stop shop” for the complete clinical development) or a specialist provider such as a Phase I Unit or Central Laboratory. There are of course differences in audit activities when considering the detailed review of the CRO’s services.

The process for a CRO audit follows the same format as for other audits, that is, preparation of the Audit Plan, conduct of the audit and reporting of the audit.

#### **5.4.1 Preparation and Notification**

The CRO should be notified within a reasonable period of the audit taking place. Most CROs require a notification period of at least 2 weeks to enable them to schedule in the audit around ongoing activities, and to ensure that the correct personnel are available on the day. Notification of the audit including the audit date, together with a draft agenda, should be sent in writing by the auditor to the CRO. This will enable the CRO to start preparations for the audit. Larger CROs often host several audits per month.

The sponsor’s QA department (or independent auditors working on behalf of the sponsor) should have SOPs and standard worksheets available for the conduct of CRO audits. The SOPs should specify the documents that need to be obtained in order to prepare for the audit. These might include:

- Index of SOPs and/or copies of the SOPs being used
- Organisation chart(s)
- Promotional material – to include facility layout and type of services offered
- The contract or an overview of the contractual requirements
- Protocol (plus any Amendments), Informed Consent documents, Investigator Brochure, blank CRF (if a clinical study is to be contracted out).

The Audit Plan should be prepared using the above information. The plan should contain details of where and when the audit will take place, the audit activities that will be carried out and contact details of the auditor and CRO personnel hosting the audit. The Audit Plan should be reviewed and signed-off by the auditor and also by QA/Clinical Management, depending on the policy of the sponsor company.

#### **5.4.2 Conduct**

The format of a CRO audit is usually as follows:

- Pre-audit meeting with key staff to discuss the scope and the agenda
- Interviews with key staff members

- Review of requested documentation, that is policies, SOPs, personnel records, examples of deliverables to assess compliance (without breaking any confidentiality agreements)
- Tour of the facility
- Post-audit meeting to feedback the audit findings (some sponsor companies do not provide feedback during pre-contract audits).

One of the difficulties with pre-contract audits is that documentation to confirm compliance with SOPs cannot be reviewed owing to confidentiality restrictions. The objective evaluation of the CRO can only be based on a review of the policies and procedures in place, the qualifications and training of personnel, rate of staff turnover and evidence of internal quality systems.

The services/areas/processes to be audited will depend on the contractual requirements. For a full capability audit the following departments/functions would be included:

- Project management
- Contracts department
- Computer systems validation/IT
- Personnel (CV, training records, job descriptions)
- Filing and archiving procedures and facilities
- SOP management
- Quality Assurance
- Quality control systems for all functions
- Facility.

Additionally, depending on the CRO (*e.g.* Full Service CROs, Laboratories, Phase I CROs), the following may be applicable:

- Safety (reporting, pharmacovigilance, subject protection)
- Investigational product management and storage
- Medical writing
- Monitoring
- Regulatory affairs (including IRB)
- Data management
- Statistics
- Biological sample processing, handling, analysis and reporting
- Clinical equipment maintenance and calibration
- Emergency procedures, equipment and medicines
- Pharmacy
- Medical cover when subjects/patients are housed
- Suitability of facility for housing subjects/patients
- Any other services offered by the CRO as appropriate.

**5.4.2.1 Pre-Audit Meeting.** The objective of the pre-audit meeting is to introduce the auditor and present the audit agenda to the CRO's staff. The following should be ascertained at the meeting:

- Confirm if access will be granted to all relevant documentation and if copies can be taken. Any restrictions should be documented
- Request a brief overview of the CRO and services provided and/or obtain a copy of promotional material
- Request an organisation chart if not already provided

- Request the CVs, job descriptions and training records of a selection of staff to cover all job descriptions
- Request quality manual/policies/SOPs where appropriate
- Request a contact person for the duration of the audit
- If required, request a translator
- Request the authorised signature record
- If a project is involved, confirm if access will be granted to all relevant study documentation and if copies can be taken. Any restrictions should be documented.

*5.4.2.2 Interviews with Key Personnel.* A suitable representative from each of the service departments that might be contracted by the sponsor should be available for interview by the auditor. The objective of the interviews is to obtain further details about the service offered by the department concerned. The type of questions asked would include:

- details of the organisation and reporting lines;
- the quality control systems in place;
- the qualifications and training of the personnel that would be assigned to any future projects placed by the sponsor;
- monitoring of deliverables and sponsor satisfaction;
- examples of projects that have been handled by the individuals and functions being interviewed (without breaking confidentiality).

The individual would be asked to describe the procedures within their particular function which would be compared by the auditor with what is stated in the CRO's SOPs. Clarification would be sought regarding any discrepancies.

*5.4.2.3 Documentation Reviews.* The auditor would not be allowed access to any ongoing study documentation to confirm compliance with SOPs, unless there was a project already ongoing for the sponsor concerned. It is strictly forbidden by Confidentiality Agreements for CROs to share another sponsor's study documents for the purposes of audit. The documents which would be made available for audit would be:

- Policies and SOPs
- CVs of staff
- Training records
- Promotional materials
- Computer systems validation.

These documents would be assessed by the auditor for compliance with regulatory requirements for the conduct of clinical studies, and compared against best practices. The staff details would be reviewed for appropriate qualifications, prior training and level of experience in their function. Staff turnover rates should be determined either by requesting this information directly, or reviewing the time that the current staff have been in position. If there are several staff who have been with the company only a short time (*e.g.* less than 1 year) this could be an indication of high staff turnover. A CRO with a high turnover of staff is not ideal for sponsor companies owing to a lack of continuity in the conduct of studies and also these staff will be less experienced in the use of the CRO's procedures.

The review of the Computer System Validation (CSV) documentation during a pre-contract audit would be performed primarily to determine whether the CRO had validated their systems adequately, and meet the requirements of ICH GCP, FDA 21 CFR Part 11 and the FDA's Guidelines for Computerised Systems used in clinical trials.



*5.4.2.4 Facility Assessment.* A tour of the facility can provide information on the quality of the organisation and the security of the electronic and hard-copy data that they will be holding for the client. Some of the areas which should be closely reviewed include:

- IP storage areas (room temperature, fridges, freezers)
- Computer room (security, access, back-up facilities and disaster recovery)
- Archive facilities on site (paper and electronic)
- Offices including filing provisions (maintenance of confidentiality, space availability, organisation)
- Subject facilities (for Phase I Units)
- Laboratory areas (for Phase I units or central labs).

*5.4.2.5 Post-Audit Meeting and Reporting.* The post-audit meeting should take place with the managers of the departments audited. Feedback should be brief but constructive. The meeting should always start with the auditor thanking the CRO for their time and co-operation during the audit. It should be remembered that in the case of a pre-contract audit the resources for the audit have been given by the CRO voluntarily.

The level of detail of the feedback will depend on the policy of the sponsor. Some companies prefer not to provide too much information to the CROs either verbally or in a written report. Other companies are quite happy to give comprehensive feedback so that the CRO is fully aware of the sponsor's expectations should a contract be placed with them in the future.

The audit report may or may not be provided to the CRO by the sponsor. Some companies prefer the auditor to send a follow-up letter to the CRO summarising the key observations from the audit. If the sponsor has requested that the CRO provide written responses, or an action plan to the audit observations (the sponsor is usually discussing contracts at this stage), then the procedure and the timelines should be explained to the CRO.

Although the amount of information that is available to an auditor during a pre-contract audit is limited, an assessment can be made of the capability of the CRO on the basis of the documentation combined with staff interviews and a tour of the facilities. If the CRO has SOPs which are compliant with regulatory requirements, experienced and trained personnel, a quality system in place, validated and secure computerised systems, then the risk of the CRO not fulfilling their contractual obligations will be low.

*5.4.2.6 Follow-Up.* The auditor should send a thank-you letter to the CRO following the audit with an explanation of the reporting procedure (if applicable to the CRO) and whether any further action will be required. An Audit Certificate should be issued and provided to the clinical department confirming that a pre-contract audit had been conducted. Some organisations allow the CRO to receive a copy of the Audit Certificate, however this is not always the case as the presence of an Audit Certificate might be interpreted as official "approval" of the CRO's procedures.

## CHAPTER 6

# Data Audits

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This chapter examines the purpose, conduct and application of data audit within a Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) Quality Assurance (QA) programme. Sometimes referred to as an In-Life Audit, a data audit is focussed upon data compliance rather than ongoing study activities, systems and processes, or upon a final report.

## 6.1 CHANGING AND CURRENT ROLE OF DATA AUDIT

Data audit is not routinely included in a GLP (pre-clinical) or GCP (clinical) QA programme.

### 6.1.1 Pre-Clinical Quality Assurance

As previously reported by the author,<sup>1</sup> although it is not mandatory for QA to review data beyond any data checking during QA inspections or during the final report review, specific data audits may be part of a GLP QA programme.

Over the past decade companies have come to rely less upon the QA department to detect errors in data, and In-Life Data Audits are less common. This is not necessarily bad news, but a reflection of a number of changes.

Since the implementation of GLP by law has become more widespread, the defined roles and responsibilities of Test Facility Management, the Study Director and of QA have become clearer, in particular the Study Director's responsibility for the integrity and compliance of data.

Internal quality control (QC) processes have been implemented because companies have needed to make more effective use of all resources, including QA.

And, of course, there is a diminishing amount of data that is not recorded or generated electronically.

### 6.1.2 Clinical Quality Assurance

There is no widespread mandatory definition of where QC and QA audit should be applied to in clinical trial processes, and the purpose of data audit of a clinical trial has often been debated, with confusion over whether this should be considered as a QC or QA audit activity.<sup>2</sup>

Companies can eliminate the debate and confusion, by applying the following three rules to data audits within a clinical QA programme:

- (i) The audit *objectives* are clear
- (ii) The audit *scope* is clear
- (iii) Appropriate *action* can be taken as a result.



Imagine a scenario without these rules:

The project manager realises that a clinical trial database has been constructed without any check of the data, and requests a data audit. The audit objective is unclear but the project manager assumes that a 100% check of the database will be done (because there has been no other check of data by any party beforehand). The audit needs to be done in a couple of days and it is hoped that no problems will arise, as there is no time available for any corrective action.

Indeed, the three rules – clear audit objectives, clear audit scope and the ability to take appropriate action – should be applied to *all* QA audits, not just those within clinical QA, and should also be considered when assigning resources and when developing audit plans, audit standard operating procedures (SOPs) and tools for other QA activities.

## 6.2 GENERAL AUDIT PRINCIPLES

### 6.2.1 Audit Objectives

The objectives of any routine audit are:

- To determine whether there are any *standards*
- To determine whether the standards that exist are *adequate*
- To determine whether these standards are being followed.

Standards that are relevant to data audit would include general organisational or departmental standards (*e.g.* policies, SOPs, work instructions), study-specific standards (*e.g.* study plan or trial protocol, data management guidelines, QC plans, contracts or even specifications upon which regulatory approval to conduct a clinical trial has been granted) and of course regulatory standards including GLP and GCP, relevant laws and regulations.

To be adequate, as a minimum, a standard must address compliance with relevant regulations and laws. In the author's opinion, standard adequacy should also mean:

- Clarity of purpose and scope
- Leaving no doubt about who is responsible for following the standard
- Having clearly identified inputs and outputs (including requirements for records management) where necessary, with logical process flow.

To determine that standards are being followed the audit is likely to include appraisal of ongoing procedures, review of data and records, discussion with personnel and, if appropriate, appraisal of facilities. In other words, the Auditor will determine whether an auditee does what he or she says and whether that matches the written standard.

### 6.2.2 Audit Plan

The Audit Plan might be a standard plan that is followed on each occasion and defined in a QA SOP or equivalent, or a company might prefer to have an SOP that requires an individual Audit Plan tailored to each audit or audit type.

In either case, so that the Auditor, auditee and person responsible for responding to the audit know what is expected of them, the Audit Plan should include clear audit objectives and enough detail of:

- Procedures and responsibilities required to meet the audit objectives
- Scope of the audit, including any items to be sampled or that are optional
- The extent of Auditor's discretion to vary the scope if necessary to achieve the audit objectives

- The extent to which the audit will include discussion with personnel, review of ongoing processes and examination of records
- The audit reporting process
- The audit response process.

When describing the audit scope and procedures the Auditor should bear in mind the end product of the audit, that is the audit report.

An example of an Audit Plan for In-Life Audit of a stability study is provided as Appendix 1.

### **6.2.3 Auditor's Toolkit**

The Auditor may prepare some audit tools to ensure that the requirements of the Audit Plan are met and that all audit observations are accurately recorded – for example, checklists, work-sheets and reference materials (if there are any specific regulatory requirements, *e.g.* data protection laws).

### **6.2.4 Audit Conduct**

The audit should be conducted according to the Audit Plan. Although the primary focus of a data audit will be examination of data and records, discussions with personnel, appraisal of ongoing procedures and in some cases, review of facilities, might also be necessary to achieve the audit objectives.

There should be opening and closing meetings, particularly if the audit programme is new and auditees are not familiar with audits, the audit will require removal of data or personnel from daily routines, or access to electronic data. At an opening meeting, the Auditor should re-iterate the audit objectives and scope, to make sure that the auditees know what is expected of them, and to ensure adequate access to the items to be audited.

A meeting with relevant personnel at the close of the audit, to summarise audit findings, can clarify issues raised, ensure that there are no misunderstandings and if appropriate, agree to any action to be taken.

### **6.2.5 Audit Reporting**

The Audit Report should be designed so that the person responsible for responding to the audit can confirm that the audit objectives were met, and take appropriate action based upon the information provided, that is the Audit Report should include the following:

- The scope of the audit, and within that scope
- Whether there were standards present
- Whether these standards were adequate
- The extent of compliance or non-compliance with these standards
- Objective evidence to support incidences of non-compliance
- Details of any corrective action started during the audit.

Whenever a subset of items has been audited the Audit Report should make clear that corrective action might also have to apply to items that were not seen during the audit.

It is advisable to include independent peer review as part of the Audit Report production process. This can ensure that the Audit Report is clear and can be read, understood, responded to (and appropriate action taken by) a person who may not have the same intimate knowledge of the area concerned as the Auditor, fresh from the audit.

## 6.3 TYPES OF DATA AUDIT

### 6.3.1 Pre-clinical (GLP) Quality Assurance Programme

**6.3.1.1 Data Audit Concurrent with the Final Report Audit.** It is common for QA audit of a final report to incorporate audit of the data and thus the scope of the report audit typically extends beyond what is necessary to comply with GLP, that is to confirm that the methods, procedures and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the regulatory study (Chapter 18).

Many companies' SOP or Audit Plan for QA audit of the final report will include the following additional objectives:

- To check that the study was conducted according to the approved Study Plan and any amendments
- To check that the study raw data has been recorded in compliance with GLP and relevant SOP(s)
- To check that the study data are complete and internally consistent
- To check that the report contains all of the elements required by GLP and relevant SOP(s).

There are benefits in conducting a data audit concurrently with the audit of a final report:

- The experimental phase of the study has been completed, and the data have been used to write the report, so the data are likely to be readily available, logically assembled and easily accessible.
- Quality Assurance and Study Director resources can be used efficiently to fulfil both the objectives of a data audit *and* a report audit.
- The audit can provide an extra check of completeness of study data prior to transfer from Study Director custody to Archives.

There are also some disadvantages:

- The QA report audit is conducted towards the end of the last phase of study conduct, where time pressures might affect how well the objectives of a data audit can be met (Remember Rule 3: “appropriate action can be taken as a result”).
- Motivation and practicality of taking corrective action to address any findings relating to raw data records might be difficult, particularly for long-term studies.
- The volume of data can sometimes be underestimated – imagine how many metres of chart recorder are generated during a 6-year-stability study conducted under three different environmental conditions.
- For findings that are generic, or out of the Study Director's control, there may be no process for preventive action.

**6.3.1.2 Data Audit During QA Inspections.** The QA inspection of an ongoing activity or facility is intended to check for compliance with GLP and with standards that are relevant to both the activity or activities and the facility being inspected – such standards might include SOPs, laboratory methods and the study plan (Chapter 17).

During the inspection, data will be reviewed

- To check that the data that is required by Study Plan SOP or Laboratory Method have been recorded
- To check that data (or any changes to data) have been recorded correctly.

**Table 1** *Examples of application of In-Life Data Audit within a Pre-clinical QA Programme*

<i>Indication</i>	<i>Main benefit and, where appropriate, some examples</i>
Novel study types	Early reassurance of adequacy of standards and of compliance; early detection of issues
Change control	Early reassurance of compliance and of appropriate approach; early detection of issues. For example changing from lab note books to study worksheets; changing from manual to electronic raw data; operational changes (e.g. company mergers)
Critical data	Effective QA activity where it is difficult to identify critical phases in order to assign QA inspections (e.g. computer validation conducted as GLP studies)
Critical data	Audit of data that is pivotal to entire study, or where data from earlier phases can directly affect subsequent phases (e.g. baseline data in a stability study of 3 or more years' duration; protein concentrations derived by Lowry assay that are necessary for calculation of end study results; data in multi-generation toxicology studies)
System data	Audit of data that supports several studies, to avoid duplication of effort (e.g. stability chamber environmental logs)
Long-term studies	Early reassurance of adequacy of standards and of compliance; early detection of issues (e.g. carcinogenicity studies)
Non-regulatory studies	In a test facility conducting regulatory and non-regulatory studies, audit of a random sample of non-regulatory studies that would not otherwise be audited can confirm that appropriate and uniform standards are maintained
Sponsor monitoring	Confirmation of adequacy of standards and of compliance of studies conducted at third party organisations

The main benefits of conducting data audit during inspections are as follows:

- The timing of inspections makes it more practical to take corrective action to address inspection findings
- The underlying cause of any issues can be more apparent, making preventive action easier.

In contrast, the location and duration of an inspection might mean that a very small sample of data is checked, it might not be possible to check internal consistency of study data (with items held elsewhere) or to check for data completeness.

**6.3.1.3 In-life Data Audits.** Owing to the disadvantages of conducting data audits concurrently with report audits, and since it is not a mandated QA activity, companies have the choice of including In-Life Data Audits where it is appropriate to their own QA programme – examples of application are shown in Table 1.

## 6.3.2 Clinical (GCP) QA Programme

On each occasion that the Auditor is preparing for a clinical audit, it may be necessary

- to confirm which standards are applicable;
- to confirm who is the person responsible for responding to the audit.

This is because the Sponsor of many clinical trials, even the most straightforward Phase I study, may transfer tasks or responsibilities under contract to Contract Research Organisations (CROs), consultants and other contractors. Furthermore, the unique nature of any clinical trial means that it is a project-driven rather than process-driven activity, which means that project-specific standards are likely. An example of general and study-specific standards applicable to the development of a clinical trial database is included in Table 3.

**Table 2** *Examples of data and records relevant to site audits*

<i>Investigator site</i>	<i>Clinical laboratory</i>
Investigator site file (essential regulatory documents)	Organisational structure
Signed subject consent forms	Records to demonstrate validity of analytical methods and participation in quality assessment schemes
Source documents	Records to demonstrate that personnel understand and accept responsibilities, and have adequate training and experience to fulfil responsibilities
CRFs	Requests for analyses
Records demonstrating fitness for purpose of equipment including computer systems	Analytical data
Records demonstrating fitness for purpose of IMP storage facilities and IMP accountability	Records demonstrating equipment fitness for purpose (analysers, balances, controlled storage units, computer systems), for example validation, correct operation, maintenance/cleaning/servicing, calibration, troubleshooting
Sample accountability	Records demonstrating fitness for purpose of facility, reagents, sample collection kits and other materials
Disclosure envelopes (where appropriate)	Sample accountability and disposition
	Analytical reports

**Table 3** *Examples of standards, records and data relevant to a database audit*

<i>Database Standards</i>
GCP, relevant regulations, data protection laws
Trial protocol
Data management SOPs
Study data management guidelines
QC plans
<i>Records demonstrating compliance:</i>
Database development – database design, construction, validation and implementation
<i>Data management:</i>
<ul style="list-style-type: none"> <li>• CRF management and tracking</li> <li>• Data entry</li> <li>• Data validation</li> <li>• QC procedures</li> <li>• Query management</li> <li>• Database locking</li> <li>• Transfer of records and files</li> <li>• Data handling report</li> </ul>
<i>Data compared before and after the transformation process:</i>
Sample of data within database listings checked against input (usually completed and approved CRF)

At the time of writing, the type and frequency of clinical audits are not mandated. The most commonly conducted audits in a clinical QA programme all include audit of data, that is trial master file audits, study site audits and database or report audits.

**6.3.2.1 Trial Master File Audit.** The trial master file (TMF) contains, as a minimum, the Sponsor's copy of the *Essential Documents* that are generated during the study. It is intended to be an up-to-date and accurate source of information for the Sponsor, to facilitate study management and to confirm correct study conduct. The TMF is the focus of GCP regulatory inspections to confirm the validity of the trial conduct and the integrity of data collected. In addition to essential documents, the TMF will often include project management records (*e.g.* appointment of personnel to study responsibilities, listings or references to SOPs for study activities, job descriptions and training records; project meeting minutes and status reports).

In addition to the objectives of any audit, a TMF audit should include assessment of file completeness (up to the point of audit) and internal consistency, particularly if the TMF is not held centrally during study conduct (*e.g.* a multi-centre study or a study with more than one organisation undertaking responsibilities on behalf of the Sponsor). Some applications of TMF audits are described in Table 4.

**Table 4** *Examples of application of In-Life Data Audit within a clinical QA Programme*

<i>Indication</i>	<i>Main benefit and, where appropriate, some examples</i>
Project management	Confirmation of appropriate documentation of transfer of responsibilities, standards applicable to the study and other project-specific records ( <i>e.g.</i> project-specific training). May be conducted as part of Initiation TMF audit (see below)
Project management	Audit of selected project management records to help to deploy QA resources effectively. For example audit of Monitoring Visit Reports to identify potential investigator sites for audit.
Initiation TMF audit	Confirmation of appropriate site selection; confirmation of procedures to ensure investigator knowledge of IMP, Protocol and obligations; confirmation of appropriate approvals required to initiate study; confirmation of practices and procedures with commitments made in regulatory authority application
During study TMF audit	Assessment of study compliance and of procedures to take action to address non-compliance; assessment of procedures for handling updates
Study closing TMF audit	Confirmation of end-of-study procedures, and completeness, compliance and consistency of TMF before transfer to archives
Change control	Early reassurance of compliance and of appropriate approach; early detection of issues. For example implementation of new processes to comply with changing regulatory requirements or operational changes ( <i>e.g.</i> company mergers)
Inherited studies	Appraisal of compliance and completeness before acceptance. For example audit of the TMF where some or all of the Sponsor's responsibilities have been transferred from one organisation to another during a study.
System data	Effective deployment of QA resources; overall appraisal and understanding of a system that is not possible from individual study audits or that extends beyond studies; permits better understanding of issues or sources of issues, including those that have been identified during study audits. Can provide information that helps improvement. Examples of systems include project management, contracting, QA, IMP management, investigator site compliance and monitoring, training, computer system management, pharmacovigilance, data management, statistical analysis, report writing, regulatory submission and archiving
Sponsor monitoring	CRO and contractor or sub-contractor election and management, to confirmation of adequacy of standards and of compliance at third party organisations

**6.3.2.2 Site Audit.** Audits at potential or participating study sites might include detailed appraisal of facilities and/or processes in order to achieve the audit objectives. However, examination of data and records will *always* be necessary, and may include data that is indigenous to the site as well as records created specifically for a clinical study.

Examples of data and records relevant to an audit at an investigator site and at a clinical laboratory are included in Table 2.

**6.3.2.3 Database or Report Audit.** A database audit or report audit is intended to determine that adequate standards exist and are being complied with for the handling and transformation of study data or for the production of a study report.

In either case, the audit will include the following:

- Examining records which demonstrate compliance with these standards
- Review of study data or the report product, and often
- Comparison of data before and after the transformation process.

Examples of standards and of records and data relevant to a database audit are included in Table 3.

Within these examples of audit and other audits that may be included within a clinical QA programme there are other possible applications of In-Life Data Audit. Some examples are listed in Table 4.

## 6.4 CONCLUSION

The conduct of a data audit is not mandatory. Its role has changed within a pre-clinical QA environment, and there has been some debate and confusion over whether this should be considered as a QC or QA audit activity within a clinical environment.

The objectives and process for conduct of a data audit are the same as for any audit type, and confusion can be eliminated by applying three rules:

- (i) The audit *objectives* are clear
- (ii) The audit *scope* is clear
- (iii) Appropriate *action* can be taken as a result.

This chapter has reviewed the various and common data audit activities, and the author suggests a number of applications of data audit within a pre-clinical or clinical QA programme.

## APPENDIX 1: EXAMPLE OF AUDIT PLAN, STABILITY STUDY

<b>Audit Plan</b> <b>Stability Study In-Life Data Audit</b>	
Compliant with: current QA SOP for Data Audits	
Approved by Head of QA, for use by all QA staff	Signature: Date: Version:
The Audit Plan applies to all stability studies within the GLP Test Facility	
The Head of QA must approve alterations to the Plan considered necessary to achieve the Audit Objectives.	
<b>Audit Objectives:</b> Identify the standards: Study Plan, SOPs and Analytical Method(s) relevant to the study being audited. Assess the extent to which these standards meet the requirements of GLP and relevant company policies. Assess whether the study is being conducted in compliance with these standards.	
<b>Audit Scope:</b> For a defined study period, include records of Correspondence, Notes to File, Standards Preparation, Sample Preparation, Study Book (observations, e.g. appearance, pH, chromatography conditions, references to other relevant records, Chromatograms. Identify any items that will be audited that are outside the Study File, e.g. equipment logs, equipment validation, standards characterisation data, stability cabinet log books, personnel training files.	
<b>Audit Preparation:</b>	
Auditor	Refer to the QA audit schedule, confirm the study to be audited. Arrange (a) date(s) for the audit with the Study Director. Review QA records relevant to the study, including Study Plan, correspondence, any previous audits and inspections.  Confirm the nature and location of any relevant data outside the Study File and arrange access.
Study Director/Principal Investigator	Confirm access to data and availability on agreed audit date(s).
<b>Audit Conduct:</b>	
Auditor	Open the audit by meeting with the Study Director/Principal Investigator and Analyst responsible for the work, confirm audit objectives and timetable. Draw up an audit checklist that corresponds with the Stability Study File Index. This should be used to confirm that all relevant data items are checked, and to record any items that have been sampled. Add to the checklist any items that will be audited that are outside the Study File.  Obtain copies of the SOPs and Method(s) relevant to the time frame of the study.  Work systematically through the data.  Close the audit by meeting with the Study Director/Principal Investigator and Analyst, to review all items of non-compliance, and if appropriate, agree any corrective action.



<b>Audit Reporting:</b>	
Auditor	<p>Select appropriate audit report template from the QA library. For In-life Stability Data Audit the audit report must contain:</p> <p><b>Summary page</b> – include study number and title; list the standards that were reviewed, describe the scope of the data audit (e.g. “all data from 3-month analyses”); list any data that have been sampled and any items of non-compliance; include audit start and finish dates and auditor signature.</p> <p><b>Audit observations</b> – present audit observations in separate sections corresponding to the standards examined, the Study File Index and nature of any items outside the Study File. Report any standards that are not compliant with GLP and Company policies, report any data are non-compliant with a standard, including reference to the standard; identify the sample that has been checked where data have been sampled, and whether make clear that corrective action will apply to items that were not seen during the audit; note any corrective action that had started during the audit or had been agreed at the closing meeting.</p> <p>Circulate the audit report to the Study Director/Principal Investigator and Head of Stability within a maximum of 2 days of audit completion; retain a QA file copy.</p> <p>If necessary, arrange a meeting with the Study Director to review audit observations and facilitate appropriate action.</p>
Study Director/Principal Investigator	<p>Provide a written response to the Auditor within 5 days of receipt of the Audit report. If necessary, arrange a meeting with the Auditor to review audit observations and facilitate appropriate action.</p>
Head of Stability and Head of QA	<p>If required agree any additional actions that are required to ensure appropriate action is taken in response to the In-Life Stability Data Audit.</p>

## REFERENCES

1. J.V. Birnie, *Data audits*, in *Good Laboratory and Clinical Practices*, P.A. Carson and N.J. Dent (eds), 1990, Chapter 10 (Superseded by this volume).
2. British Association of Research Quality Assurance Chat Lines (mailing lists), 2002–2003.

## CHAPTER 7

# Research Ethics Committees

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### 7.1 A BRIEF HISTORY OF THE REGULATION OF MEDICAL RESEARCH

The regulation of medical research dates back to 1900. Since then, and particularly during the last 30 years, there has been a significant growth in the writing of regulations, codes of practice, guidelines and laws.

The development of research ethics in the 20th century appears to be based on a recurring cycle of scandal, leading to outcry, and then to regulation. For example, recognition of the abuse of human rights in medical experiments, famously in the Nazi concentration camps,<sup>1</sup> or later in the Tuskegee syphilis study<sup>2</sup> resulted, respectively, in the writing of the Nuremberg Code in 1947 and the US National Research Act in 1974. Maurice Pappworth's exposé of the amount of research being carried out without the knowledge or consent of research subjects in the United Kingdom was followed by the first guidelines published by the Royal College of Physicians in 1967.<sup>3</sup>

In 1966, the US Public Health Service stipulated that there must be ethical review of all research it funded, and in 1974 the US National Research Act required ethical review by Institutional Review Boards (IRBs) of all federally funded research.

But however good the intentions, the drawing up of regulations and the implementation of IRBs cannot, in themselves, guarantee good practice.

There have been several recent high profile, temporary shutdowns of some of the largest medical research programmes in the United States, where regulations were not followed after unsatisfactory ethical review by the institution's IRB. For example, in July 2001, the US Food and Drug Administration (FDA) found researchers from Johns Hopkins University guilty of violating safety procedures in an asthma study that resulted in the death of a healthy volunteer.<sup>4</sup> Later, in the same year, the judge at the Maryland Court of Appeal likened a study of different ways of getting rid of lead paint in homes, during which children were knowingly exposed to high levels of lead, to the Tuskegee experiment.<sup>5</sup>

The United Kingdom has not been without its research scandals, despite its having had a system of local research ethics committees (LRECs) since 1966 and multi-centre research ethics committees (MRECs) since 1997. In North Staffordshire in the late 1990s, parents of premature babies reported that their babies had been put into a research study of a ventilator without their knowledge or consent.<sup>6</sup> At Liverpool's Alder Hey Children's Hospital, 2080 organs were removed from 800 children without their parents' knowledge, purportedly for research.<sup>7</sup>

There appears, now, to be an increasing awareness of the necessity of appropriate training of ethics committee members and clear operational procedures to complement the regulations. The

United States is moving towards closer regulation of the process of ethical review by methods such as the certification of IRB administrators and compulsory training in research ethics for researchers.

In the United Kingdom, the publication of the Governance Arrangements for NHS Research Ethics Committees (RECs) in 2001, with its stipulation that members must agree to take part in initial and continued education, and clear guidelines on the responsibilities of ethics committees, is a first step in the process of tightening up procedures, which will hopefully result in a reduction of research violations. There is also now a system of accreditation of RECs.

## 7.2 KEY RESEARCH ETHICS GUIDELINES

Another factor which seems to be making some difference to the quality of ethical review in medical research, and which has recently been highlighted by a well-respected commentator on research ethics, is the commercial pressure exerted by the pharmaceutical industry to ensure that Good Clinical Practice (GCP) standards are applied wherever pharmaceutical research is undertaken, to satisfy regulatory agencies. This has been mediated through various transnational guidelines which individual countries have subsumed as laws or regulations.<sup>8</sup>

One of the key transnational guidelines is The Declaration of Helsinki.<sup>9</sup> This document was published by the World Medical Association in 1964 and amended in 1975, 1983, 1989 and 1996. It was most recently revised in 2000. The Declaration of Helsinki lays out general principles, rather than precise rules. Most researchers, when submitting a research proposal, will cite this very important document as the one to which they have referred. It is somewhat disturbing to note how many of them are unaware of the more recent revision, and how few appear to have actually read the Declaration in its entirety.

Another key guideline is the 1996 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline for GCP – otherwise known as ICH GCP. Good clinical practice is defined as

An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.<sup>10</sup>

There are a number of other useful guidelines. These include the Council For International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects<sup>11</sup> which are particularly useful for researchers involved in international research, and the set of guidelines produced by the Association of Pharmaceutical Industry (ABPI).<sup>12</sup>

Useful guidance on research ethics is also provided by the Royal Colleges, including the Royal College of Paediatrics and Child Health,<sup>13</sup> the Royal College of Psychiatrists,<sup>14</sup> the Royal College of Pathologists,<sup>15</sup> the Royal College of Physicians<sup>16</sup> and the Royal College of Nursing.<sup>17</sup>

## 7.3 LEGISLATION AND ETHICAL REVIEW

None of the official publications mentioned above have the same legal force as legislation. Similarly, RECs do not have the legal status of a statutory body, with clearly defined legal powers and duties. Any authority that an Ethics Committee wields is therefore informal and extra-legal. However, as leading medical lawyers point out, such authority should not be underestimated.

Within the National Health Service, the *Governance Arrangements for NHS Research Ethics Committees* (GAFREC) places a clear responsibility upon Health Authorities to set up,

support and monitor NHS Local Research Ethics Committees, and the Department of Health's document, *The Research Governance Framework for Health and Social Care* (2001), states: 'The Department of Health requires that all research involving patients, service users, care professionals or volunteers, or their organs, tissue or data, is reviewed independently to ensure it meets ethical standards.' (para 2.2.2) Therefore, although there is no clear legal obligation on a potential researcher to submit a protocol to an Ethics Committee for approval, researchers within the NHS will be denied access to patients and data without such approval. Furthermore, those who fund research ordinarily stipulate that research must be approved by a Research Ethics Committee if it is to be funded. In relation to the publication of research, it is standard practice, at least in English journals, for editors not to publish research results if proper approval was not sought or given.<sup>18</sup>

While it is not the function of RECs to provide legal advice, or to provide authoritative resolution of legal issues, even if the committee has members with legal expertise,<sup>19</sup> once an REC constitutes itself and reviews research proposals, it takes on legal duties that derive from the central purposes of the Committee: to protect the dignity, rights, safety and well-being of all actual or potential research participants.<sup>20</sup>

## 7.4 THE ROLE AND RESPONSIBILITY OF NHS RESEARCH ETHICS COMMITTEES

The primary responsibility of RECs is the protection of research subjects from harm. They also serve to facilitate valid and worthwhile research.

The purpose of ethical review by RECs is to ensure that all issues relating to informed consent have been addressed, that there is equitable selection of research subjects and a favourable balance of harms and benefits. Additionally, review should ensure that the design of the research is sound, that the investigators are competent and that there are arrangements for compensation in the event of research-induced injury.

Under GAfREC,<sup>21</sup> Ethics Committees have a clear remit to provide ethical advice for any research proposal involving:

- patients and users of the NHS;
- relatives or carers of patients and users of the NHS;
- access to data, organs or other bodily material of past and present NHS patients;
- foetal material and IVF involving NHS patients;
- the recently dead in NHS premises;
- the use of, or potential access to, NHS premises or facilities;
- NHS staff recruited as research participants by virtue of their professional role.

GAfREC set out in detail the general principles and standards relating to the role of RECs, their remit, establishment and support, and membership requirements and process. They also detail the composition of RECs, the working procedures, the process of ethical review of a research protocol and what is involved in the submitting of an application. The document should be read in conjunction with the Research Governance Framework for Health and Social Care.<sup>22</sup>

For the purposes of this chapter, the key issues within GAfREC have been extracted, and, where appropriate, summarised. The numbers in brackets refer to the relevant sections of the document, the full version of which can be seen at <http://www.corec.org.uk/recs/guidance/guidance.htm#gafrec>. GAfREC is currently being revised by the Department of Health.

The document, Governance Arrangements for NHS RECs in Scotland is available at <http://www.show.scot.nhs.uk/cso>.

## **7.5 ESTABLISHMENT AND SUPPORT OF NHS RESEARCH ETHICS COMMITTEES**

NHS RECs in England may only be established and governed by Health Authorities or the Department of Health. Health Authorities are accountable for the establishment, support, training and monitoring of all NHS LRECs within their boundaries. (Sections 4.1, 4.2)

In 2002, the previous Health Authorities in England were replaced by 28 new and larger Strategic Health Authorities. These Strategic Health Authorities were created by the Government to manage the local NHS on behalf of the Secretary of State. In 2006, the number of Strategic Health Authorities was reduced to 10.

For the purposes of ethical review by NHS RECs, a research site is defined in the Standard Operating Procedures (SOPs)<sup>23</sup> as the single organisation or operating unit responsible for conducting the research at a particular locality. In most cases this will be an acute NHS Trust, a NHS Partnership Trust or a GP practice. (SOP 4.11–4.12)

The Strategic Health Authority is responsible for the appointment of REC members. Appointment of members is by an open process; vacancies must be filled following public advertisement in the press, and/or by advertisement via local professional and other networks. Members are normally appointed for fixed terms, normally of 5 years. Terms of appointment may be renewed, but more than two consecutive terms should not normally be served on the same REC (Section 5.10).

## **7.6 MEMBERSHIP REQUIREMENTS AND COMPOSITION OF NHS RESEARCH ETHICS COMMITTEES**

An REC should have sufficient members – maximum 18 – to guarantee the presence of a quorum at each meeting. (Section 6.1) A quorum must consist of seven members which includes the chair or vice-chair, at least one “expert” member with the relevant clinical and/methodological expertise, one “lay” member and at least one other member who is independent of the institution or specific location where the research is to take place (Section 6.11).

RECs should have a balance of members in terms of age and gender, “lay” and “expert” members, and efforts should be made to recruit members from black and ethnic minority backgrounds as well as people with disabilities (Sections 6.2, 6.3).

The “expert” members of the committee should be chosen to ensure that the REC has the relevant methodological and ethical expertise in clinical and non-clinical research and qualitative or other research methods applicable to health services, social science and social care research. The REC should also have expertise in clinical practice and include members who are hospital and community staff and doctors who are in general practice. An REC must also include members with expertise in statistics relevant to research, and pharmacy (Section 6.4).

At least a third of the membership must be “lay” members who are independent of the NHS and whose primary personal or professional interest is not in clinical research. Lay membership can include non-medical clinical staff who have not practised their profession for at least 5 years, but at least half the “lay” members must have no background in health or social care and must never have been involved in carrying out research involving human participants, their tissue or data (Sections 6.5, 6.6, 6.7).

## **7.7 WORKING PROCEDURES OF NHS RESEARCH ETHICS COMMITTEES**

In February 2004, the Central Office of Research Ethics Committees (COREC) published its SOPs. v1. SOPs are now v3.1. These SOPs meet the obligations of the United Kingdom under Directive 2001/20/EC of the European Parliament and the Council of the European Union (“the EU Directive”) for the operation of ethics committees in relation to Clinical Trials of Investigational

Medicinal Products (CTIMPs). The provisions of the EU Directive include the implementation of recognised principles of GCP in the conduct of CTIMPs (see Chapter 9).

Under the Regulations as set out in the SOP, a decision should be reached and communicated to the applicant within 60 calendar days of the submission of a valid application. (SOP 3.1). After an initial review, any further written information or clarification may be requested from the applicant on one occasion only. During this period, the time-frame is suspended and does not recommence until a satisfactory response is received. Substantial amendments made after the research has started require a favourable opinion from the REC that approved the original study (“the main REC”). Notices of substantial amendment may be reviewed at a sub-committee meeting. Minor amendments may be made without notifying the main REC (Section 5 of SOPs).

Ethical review by the REC should take place at the same time that management approval is being sought from the relevant NHS host organisation (normally the Research and Development Directorate) and any relevant regulatory authorities such as the Medicines and Healthcare products Regulatory Agency (MHRA).

### **7.7.1 Follow-Up and Reporting Procedures**

The sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take urgent safety measures in order to protect the research subjects against any immediate hazard to their health or safety. The main REC must be notified immediately and in any event within 3 days that such measures have been taken and the reasons why. (SOP 9.20)

A sponsor or Chief Investigator may make other minor deviations from a protocol to deal with unforeseen circumstances. These do not need to be routinely notified to the main REC. However, if a deviation would meet the criteria for a “substantial amendment”, it should be submitted to the main REC for ethical review. A distinction is drawn between “protocol deviations”, which are made with the permission of the sponsor or Chief Investigator, and “protocol violations”, which are made as a result of error, fraud or misconduct. Where the sponsor or Chief Investigator considers that a protocol violation has occurred, they should notify the main REC as soon as the matter comes to their attention. An explanation should be given and the main REC informed as to what further action they plan to take. (SOP 9.67–9.70)

The main REC may review the favourable ethical opinion at any time in the light of progress or safety reports, or any other information it receives about the conduct of the research. Consideration may be given to suspending or terminating the favourable opinion where serious concerns arise. (SOP 9.71–9.77)

Other than by means of required progress reports that are detailed in GAfREC, the REC has no responsibility for pro-active monitoring of research, the accountability for which lies with the NHS host organisation (Section 7.33).

While most researchers are honest and conscientious, research fraud and misconduct are sadly not an unknown phenomenon.<sup>24</sup> A member of an REC who becomes aware of a possible breach of good practice in research is expected to report this initially to the Chair and Co-ordinator of the REC, whose duty it is to inform the OREC manager who, in consultation with the Operations Director at COREC and the appointing authority will decide whether the information should be shared with other bodies so that the matter can be formally investigated (Section 9.89–9.94).

### **7.7.2 The Process of Ethical Review of a Research Proposal**

According to GAfREC, the primary task of an REC lies in the ethical review of research proposal and their supporting documents. Special attention should be given to the nature of any intervention and its safety for participants, to the informed consent process, documentation, and to the suitability and feasibility of the protocol (Section 9.7).



The Research Governance Framework makes it clear that the sponsor is responsible for ensuring the quality of the science. It is not the remit of an REC to undertake additional scientific review, but it should satisfy itself that the review already undertaken is adequate for the nature of the proposal under consideration (Sections 9.8, 9.9).

In reviewing a research protocol, an REC should be adequately reassured about the scientific design and conduct of the study, the recruitment, care and protection of research participants, the protection of research participants' confidentiality, the informed consent process and community considerations.

In terms of scientific design, the committee will be looking for evidence that the study design is appropriate in relation to the objectives of the study. This will include statistical methodology and the potential for reaching sound conclusions with the smallest number of research participants. The committee will look for justification of predictable risks and inconveniences weighed against the anticipated benefits for research participants and other patients, now and in the future. There must be a clear justification if there is to be a control arm, and details of the randomisation process. There must be written criteria for the suspension or termination of the research as a whole and details of the provisions made for the monitoring and auditing of the conduct of the research. There must be information about the adequacy of the research site, including the supporting staff, available facilities and emergency procedures. Consideration must also have been given to the manner in which the results of the research will be reported and published (Section 9.13).

The REC will need to be reassured about all issues relating to the recruitment, care and protection of research subjects. The committee will require information on the characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status and ethnicity) and the justification for any decisions made in this respect. There must be information on how initial contact with participants will be made, how information will be conveyed to potential research participants and details of any inclusion and exclusion criteria (Section 9.14).

Details on the safety of any intervention to be used in the proposed research must be given, including information on the suitability of the investigator's qualifications and experience for ensuring good conduct of the proposed study. If there are plans to withhold and withdraw standard therapies, these must be detailed, as must the adequacy of the health and social care to be provided to research participants during and after the course of the research. Arrangements for informing research participants' general practitioner, if appropriate, and with the consent of the research participant must be in place. There must be a description of any plans to make the study product available to research participants after the research, of any financial costs to research participants and any rewards and compensations. Insurance and indemnity arrangements must be described, as must the nature and size of any grants or other payments to be made to any researchers or host institutions, including details of any circumstances that might lead to conflicts of interests (Section 9.15).

Protection of research participants' confidentiality is of paramount importance. RECs will look for a description of the people who will have access to personal data, including medical records and biological samples. They will require information on how confidentiality will be ensured, how far information will be anonymised, and how long, and where, data and samples will be kept (Section 9.16).

The informed consent process is taken extremely seriously by REC members. There needs to be a full description of the process for obtaining informed consent, examples of the written and oral information to be given to the research participant, clear justification for the inclusion of individuals who cannot consent and a full account of the arrangements for obtaining consent or authorisation for the participation of such individuals. RECs will want to be reassured that researchers understand that information-giving and consent is not a one-off occurrence but a continuous process (Section 9.17). Poor quality participant information sheets are one of the main reasons that protocols are returned to researchers for improvement. Researchers should seek advice on how to write clear and accurate written information.<sup>25</sup>

### 7.7.3 Submitting an Application

Application forms are now available on the COREC website ([www.corec.org.uk](http://www.corec.org.uk)). This site also provides detailed guidance for applicants to RECs.

Since April 2004, the original system of LRECs and MRECs has undergone considerable revision. There are now essentially two types of RECs.

- (i) RECs that are “recognised” under the Clinical Trials Regulations by the United Kingdom Ethics Committee Authority (UKECA) to review CTIMPs. There are three types of “recognised” REC. The recognised RECs are mainly NHS RECs but include some privately established committees outside the NHS that have historically formed the main system of review for Phase 1 drug trials in healthy volunteers. Since 1 May 2005 non NHS committees are required to comply fully with the provisions of Schedule 2 of the Regulations relating to the operation of ethics committees. Recognised NHS RECs may review other NHS research as well as CTIMPs. They therefore have a dual status deriving from the Regulations (which provide the statutory basis for review of CTIMPs) and from GAFREC (which provide a basis in guidance for review of other research).
- (ii) NHS RECs that are not recognised by UKECA. These are called “authorised” committees. Authorised committees are not legally recognised to review CTIMPs but under GAFREC may review any other NHS research involving human subjects.

Details of the types of RECs are available on <http://www.corec.org.uk/applicants/apply/apply.htm#which>.

To which REC a researcher will need to apply will depend on the type of research being undertaken:

- *Phase 1 clinical trial of a medicinal product in healthy volunteers only.* Researchers will need to apply directly to a *Type 1 recognised REC*. It may not be necessary to complete the standard NHS REC application form if using a non-NHS REC.
- *Clinical trial of a medicinal product (other than a Phase 1 trial in healthy volunteers only) taking place in a single domain.*

Researchers should use the central allocation system (CAS) (<http://www.corec.org.uk/applicants/apply/cas.htm>) to book their application with the relevant *Type 2 recognised REC* for that domain.

- *A clinical trial of a medicinal product (other than a Phase 1 trial in healthy volunteers) taking place in more than one domain.*

Researchers should use the CAS to book their application with a *Type 3 recognised REC*.

- *Research involving adults with incapacity in Scotland as research participants.*

Where the research is a CTIMP and the Chief Investigator is professionally based outside Scotland, the Regulations allow for the application to be reviewed by any recognised REC (which would need to be *Type 3* as it is multi-domain). If the Chief Investigator is based in Scotland, the Regulations require that the application is reviewed by the committee constituted by Scottish Ministers under the Adults with Incapacity (Scotland) Act 2000, which is MREC for Scotland Committee A. Where the research is not a CTIMP, it will always be allocated to MREC for Scotland Committee A if there is one or more sites in Scotland, even where the CI is based outside Scotland.

- *Research involving prisoners or young offenders as research participants.*

Researchers should use the CAS to book their application and will be allocated a suitable REC.

- *A project that is not a clinical trial of a medicinal product, does not involve prisoners as research participants and will take place within a single domain.*



Researchers should apply directly to any REC in that domain (except non-NHS Type 1 RECs and MRECs). A geographical list of all RECs in the UK arranged by domain is available on the COREC website.

- *A project that is not a clinical trial of a medicinal product does not involve prisoners as research participants and will take place in more than one domain.*

Researchers should use the CAS to book their application and will be allocated a suitable REC.

Site-Specific Assessment (SSA) is required as part of the ethical opinion. The Principal Investigator should apply to the local REC by completing the “site information” section of the application form. The application for SSA can be made once Part A and B of the application have been submitted to the main REC and been accepted as valid for review. The SSA will either be carried out by the REC or referred for advice from the local NHS R&D office, depending on local arrangements for SSAs. The outcome of the SSA will be notified to the main REC within 25 days and approval for the Site and Principal Investigator may then be issued by the main REC to the chief investigator.<sup>26</sup>

An integrated “site information” dataset, containing the current Part C (used for SSA) and the R&D application form is in development.

## 7.8 DOCUMENTATION

All documentation required for a thorough and complete review of the ethics of proposed research should be submitted by the applicant. (SOP 1.48) This may include, but is not limited to

- signed and dated application form;
- covering letter;
- the protocol of the proposed research together with supporting documents and references, and details of any previous scientific peer review;
- a summary, synopsis or flowchart of the protocol in non-technical language;
- diary cards or other questionnaires intended for research participants;
- when the research involves a study product (such as a pharmaceutical or device) an adequate summary of all safety, pharmacological, pharmaceutical and toxicological data available on the study project to date;
- the applicant’s current CV, signed and dated;
- material to be used (including advertisements) for the recruitment of potential research participants;
- a full description of the process of obtaining and documenting consent;
- written and other forms of information for potential research participants in the language understood by the potential research participants and, when required, in other languages;
- informed consent form in the language understood by the potential research participants and, when required, in other languages;
- a description of the arrangements for insurance cover for research participants, if applicable;
- a statement of agreement to comply with ethical principles set out in relevant guidelines, and the identity of such guidelines;
- all significant previous decisions (*e.g.* those leading to a negative decision or a modified protocol) by other RECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modifications to the protocol made on that account. The reasons for previous negative decisions should be provided (Section 10.6).

All documentation should detail the version number and dates.

Despite the recent proliferation of guidelines on the ethical conduct of research and the increasing amount of information supplied to researchers by RECs and COREC, the research proposals which are given favourable ethical opinion by ethics committees on their first submission without any queries or requests for amendments, are in a minority.

There is a conflict between the demands of pharmaceutical companies, with their lengthy and complex patient information booklets and insistence on a signature as the primary evidence of consent, and the requirements of the RECs with their rightful insistence on clear, appropriate and simple information and evidence of a commitment to a process of informed consent.

Whatever the demands of the pharmaceutical companies, an REC will not approve any piece of research, however important and potentially useful to society, unless the researcher has ensured that the information provided to the research participant is appropriate. It is also the duty of the researcher to ensure that the whole research proposal, not just the parts destined for the research participants, is comprehensible to a committee comprising both clinical and lay members.

These demands may well result in an increased workload for researchers but will ultimately ensure a smooth journey through the ever more complex REC system.

The role of QA in the Ethics process primarily is to provide assurance that:

- trial proposals have received a favourable opinion by an appropriate REC;
- the REC is properly constituted and trained;
- the REC documentation is complete and securely stored;
- REC procedures are being implemented.

Some elements of Phase I RECs that QA should check are summarised in Chapter 11.

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## CHAPTER 8

# Good Clinical Practice/Good Manufacturing Practice (GCP/GMP) Interface, Investigational Product Accountability

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## 8.1 INTRODUCTION

Clinical trial supplies management and drug accountability are important parts of the integrity of any clinical trial. It is important to establish that the correct amounts and dosage forms of the investigational and comparator drugs, as specified in the protocol, were received by the clinical investigator, and that these were accurately dispensed to the patient. The clinical investigator must keep accurate and up-to-date records of all supplies-related activities, and the records must be inspected to verify the drug accountability. In outline, the type of items that should be inspected are the number of doses/packs manufactured, shipped and stocked, the prescription of the drug and the amounts returned by trial subjects or destroyed. There should also be a check on the storage conditions for the drug and on the batch and formulation number to confirm that they agree with the sponsor's records.

The ICH good clinical practices (GCPs) give us a working definition of investigational product:

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used as assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.<sup>1</sup>

This definition fully embraces the US FDA definition of investigational drug and investigational new drug, which is given as

“A new drug, antibiotic drug, or biological drug that is used in a clinical investigation”.<sup>2</sup>

An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the human body.<sup>3</sup>

The Medicines for Human Use (Clinical Trials) Regulations 2003 (MHUCT Regs) defines an investigational medicinal product as ‘a pharmaceutical form of an active substance as placebo being tested, or to be tested or used, or to be used as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial (a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, (b) used for an indication not included in the summary of the product

characteristics under the authorisation for that product or (c) used to gain further information about the form of that product as authorised under the authorisation.

The good clinical practice/good manufacturing practice (GCP/GMP) interface is where investigational products for use in clinical trials are manufactured in relatively low volumes and are packaged, labelled, distributed, prescribed, dispensed and finally ingested or absorbed by clinical trial subjects. There are four components for the professional Quality Assurance (QA) auditor to consider at this interface:

- (i) Provision of the investigational product by the trial sponsor including:
  - manufacture
  - packaging
  - labelling
  - shipping
- (ii) Management of the investigational product at the trial site including:
  - receipt by the investigator
  - storage by the investigator or pharmacist
  - prescription by the investigator
  - dispensing by the investigator or pharmacist
  - reconciliation and accountability by the investigator or pharmacist
- (iii) Monitoring of investigational product by the sponsor including:
  - drug accountability activities by the clinical research associate (CRA) or monitor
  - drug destruction or return by the CRA or monitor
  - audits by CQA auditors
- (iv) Inspection by regulatory authority inspectors.

This chapter presents these four aspects of the GCP/GMP interface from the perspective of the QA professional, explains the rationale behind the various aspects of the management of investigational products and advises on audit approaches to verify compliance.

## **8.2 THE PROVISION OF THE INVESTIGATIONAL PRODUCT BY THE TRIAL SPONSOR**

This section addresses the relevant framework of legal requirements and guideline recommendations, looks at how the professional QA auditor might review the sponsor's provision of investigational product and takes a detailed look at the complex situations that can arise with transportation of investigational product from the place of manufacture to the clinical investigation site.

### **8.2.1 How do Good Clinical Practice and Good Manufacturing Practice Interact – The Regulatory Framework**

The GMP regulations in their original form pre-date GCP considerably and so they do not refer to it. However, it is clear from annexes and amendments, and from several sections of the “Rules and Guidance for Pharmaceutical Manufacturers and Distributors 1997” (The Orange Book) that investigational product being manufactured for use in clinical trials must be made according to GMP. This is now also a requirement under the MHUCT Regs 2003.

The GMP guidelines were originally designed to apply to the bulk manufacture under license of formulated medicinal products for human or animal use – the GMP requirements for human and

veterinary uses are identical. However, they were then extended to the manufacture of active ingredients for medicinal products to be used in clinical trials and a certain amount of “retrofitting” has been necessary for the new applications. However, this progressive wider application of GMP is justified for a number of compelling reasons including concerns about the quality and safety of medicines. The manufacturing processes that produce a medicinal product of an acceptable quality, in the required quantity and in a cost-effective way are themselves evolving from drug discovery right up to and beyond clinical trials. It is reasonable therefore to expect that as a candidate drug progresses through the battery of tests from animal pharmacology, through toxicology and metabolism, to Phase I (Chapter 12) and subsequently Phase II and III clinical trials in human beings, it will be made and used in progressively improved forms – perhaps purer, safer or in different chemical forms. It may be mixed with different carriers to improve administration or to extend the shelf life. This is reflected in the following text taken from the GMP “Orange Book”:

Quality Management extends to original product design, development, formulation and preparation of medicinal products for use in clinical trials. This includes the establishment of well-defined manufacturing processes, sampling programmes and analytical test methods and appropriate specifications for ingredients, printed and unprinted packaging components and finished dosage forms.

Subsequently any pharmaceutical preparation should contain the same or a lesser range of impurities as the batch(es) used in clinical trials. It is therefore of vital importance that the quality of routine production batches should correspond to a specification derived from the composition of development batches. Ultimately the quality and safety of a medicinal product depends on the application of appropriate procedures based on GMP leading to a product within the recognised specification. Standard procedures and recognised specifications cannot be divorced.<sup>4</sup>

The “Orange Book” makes other references that make it clear that the investigational products used in clinical trials should be manufactured according to GMP.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisation referred to in Article 16 of Directive 75/319/EEC and in Article 24 of Directive 81/851/EEC as modified. They are also relevant for all other large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, **for the preparation of products for use in clinical trials**, and for wholesaling, where applicable.<sup>5</sup>

In November 2001, a new draft of Annex 13 of the Orange Book was issued for public consultation. This document strengthens the association between investigational products, GCP and GMP and includes guidance on ordering, shipping and returning clinical trials. It also references comparator and modified comparator medications and rescues medications as well as investigational ones, blinding and randomisation, labelling and re-labelling. Details are not given here because the final form may differ from the draft when the consultation phase is complete. However, it is clear that as the GMP requirements are reviewed and adjusted, there will be a progressive application of GMP to clinical trial investigational, comparator and other products largely in the interests of protecting the safety of clinical trial subjects.

With regard to GCP, the various draft GCP guidelines of the early 1990s included no requirement for the manufacture of investigational product for clinical trials to conform to GMP. This oversight was corrected by the ICH GCP guidelines, effective from January 1997, which say

“Investigational product should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP) . . . .”<sup>6</sup> and “The sponsor should ensure that the investigational product(s) . . . is manufactured in accordance with any applicable GMP . . . the labelling should comply with applicable regulatory requirements”.<sup>7</sup>



### 8.2.2 Auditing the Sponsor's Provision of Investigational Product

This sub-section does *not* deal with the requirements that GMP places on a sponsoring company during manufacture of investigational product. From the GCP auditor's perspective, there are checks that can be conducted on the packaging and labelling of the product itself and on the paperwork relating to the request for the product, its manufacture, its despatch and its certificate of analysis.

Product packaging and labelling must agree with the request form for manufacture of the supplies and with the clinical trial protocol, and auditors should check the following:

- the quantity manufactured is the same as that requested and corresponds with the requirements of the clinical trial protocol;
- the dosage form is that requested and corresponds with the requirements of the clinical trial protocol;
- the type of packaging is that requested and corresponds with the requirements of the clinical trial protocol;
- the labelling gives the drug name and dosage correctly according to the request form and corresponds with the requirements of the clinical trial protocol;
- any special storage conditions are clearly indicated on the outside of the packaging;
- any instructions for trial subjects or investigators are clearly legible, unambiguous and in the appropriate languages according to the protocol;
- the lot number is given on the labels and corresponds with the certificate of analysis.

Note that the US FDA GCP regulations require that the packaging of investigational product bears a label saying "Caution: New Drug – Limited by Federal Law to investigational use". Outside the United States, the words "United States" replaces the word "Federal" in this statement. The FDA also mandates that the labelling of investigational products should not imply that the drug is safe or effective with relation to the purpose for which it is being investigated.

Auditors should also check that the certificate of analysis complies with GMP. To do so, it must

- identify the organisation that issued it;
- be authorised by a person competent to do so and give his/her qualifications;
- name the material it refers to and identify its batch number;
- state that the material has been tested and say when and by whom;
- state the specification and methods against which and by which the tests were performed;
- give the test results or state that the results obtained showed compliance with the stated specification.

Finally, there should also be shipping documentation that the auditor can check. Shipping documentation varies enormously depending on the type of transportation used, but it should be reviewed during audit because

- it is a valuable record of the dates of events, which ought to correspond with other records available at the site and sponsor premises;
- it must correspond with any special storage conditions that may be there, for example, supplies that must be kept at low temperatures will require refrigerated transportation and requirement ought to be very clear on the despatch documentation to alert the transporter.

### 8.2.3 Transportation of Supplies to the Clinical Trial Investigational Site

When GCP auditing began in the early 1990s, a frequent finding was that sponsors would supply trial sites with investigational products while waiting to receive regulatory authority approval for the trial and/or a favourable opinion from the ethics committee. Inevitably, some investigators



started the trial before the sponsor had received either the necessary approval from the regulatory authority or the necessary favourable opinion from the ethics committee. It is unacceptable and indeed illegal under the MHUCT Regs 2003 to expose subjects to investigational medicines without the necessary approvals and, in recognition of this, the ICH GCP specifically prohibits sponsors from supplying investigational products to trial sites before all the required documentation is in the sponsor's possession. Required documentation would include a favourable opinion from the ethics committee, authorisation to proceed with the trial from the regulatory authorities and any internal approvals required by the sponsor's own SOPs.

What constitutes being in the sponsor's possession is something of a moot point. A reputable organisation will wait for receipt of the authorisations in writing before shipping drug supplies to an investigator site but some will do so on the strength of telephone conversations with regulatory authorities or ethics committees implying or inferring that approval has been given or will be issued imminently. Individual sponsor SOPs should give clarity on the position adopted by any one of the sponsor companies.

Before discussing the trial site, we should consider the fate of supplies en-route from manufacture. Even with direct shipping, the supplies might have had to pass through warehouses, airports and customs sheds and there will be very little to assure the auditor that they were appropriately handled and stored throughout. However, patterns of shipping vary and can be quite convoluted:

- manufacture direct to site
- manufacture to central site for onward distribution
- manufacture to sponsor premises for onward distribution
- manufacture to sponsor premises for onward distribution to central site for onward distribution.

Some clinical trial sponsors ship large quantities of drug from the place of manufacture to their offices in the countries where the clinical trial is to take place, or to other agreed bases – these supplies are known as “depot stock”. Here the supplies may be held for some time and they are subsequently released on a site-by-site basis as investigational sites are recruited into the trial. Where this happens, the auditor should be able to access the storage locations and the relevant documentation.

As for all investigational product storage locations, there are certain requirements and expectations to be respected. These are described fully in the following section addressing the investigational product storage locations at the investigation site.

The supplies release documentation, transit documentation, receipt documentation and subsequent shipping documentation are all internal to the sponsor, and auditors ought to have little difficulty accessing them and tracking drug movements. Most importantly, the auditor should check the following:

- dates and sequences of events should match those in other documents;
- quantities of drug at various stages of their journey can be reconciled against the total amounts shipped and received;
- any special storage requirements were provided throughout the journey.

There are some special factors that can affect drug shipment and these factors vary a great deal and require local knowledge. Auditors are advised to keep their knowledge of local and individual requirements up to date as far as possible and to check specific requirements that are relevant to particular audits they are conducting with experienced people who have local knowledge.

Some special factors known to the author are as follows:

- In some countries, investigational product that is being imported must be delivered to the address given on the import licence, even if this is not the ultimate destination of the supplies.

In these countries, if the delivery is not to this address the courier and possibly the sponsor may be deemed to have broken the law.

- In some countries, investigational product being delivered to a hospital must be taken directly to the hospital pharmacist and not to the investigator. In these countries, failure to do this would breach the relevant codes of practice, the rules of the institution and could even be technically illegal.
- In some countries, investigational product may only be released from customs to someone who is a national of that country.
- Most, if not all, customs officers have the legal right to open packages being imported. It is therefore very important that any known health and safety risks are made clear on the outside packaging of the products.
- Many customs officers are not obliged to re-package any packages they open. This means that labels, packaging materials and even quantities of investigational product may be damaged or go astray.
- Products that must be kept within a certain temperature range need some sort of monitoring to demonstrate that transportation and storage conditions were always suitable. The most convenient system is the inclusion of a max–min thermometer within the packaging alongside the investigational product that is checked upon opening the packaging. However, knowing where the temperature data will be recorded and what would happen if the recorded temperatures are outside the range might pose the auditor something of a challenge!

### **8.3 MANAGEMENT OF INVESTIGATIONAL PRODUCT AT THE TRIAL SITE**

This section addresses all aspects of investigational drug management at the investigational site including receipt, storage, prescription, dispensing and accountability and reconciliation of clinical trial supplies and some health and safety aspects. Drug accountability is the process of establishing the movements and fate of investigational and other products, and drug reconciliation compares the findings with the intended disposition of these substances according to the protocol and trial design.

GCP is unambiguous in placing with the investigator or his institution full responsibility for the investigational product while it is at the trial site. This includes storing the supplies, dispensing them, record keeping and accounting for them.

At the trial site, the auditor can expect to see enough records to re-construct the movements of study drug from arrival to the end of the trial. Shipping documentation, delivery notes and receipts given ought to indicate what was delivered, when and who took receipt of the delivery. If a hospital pharmacy was involved in the trial, there ought to be prescriptions from the investigator or his co-workers instructing the release of supplies. The supplies may be released directly to study subjects on a patient-by-patient basis, but it is more usual that drugs are released on a batch basis, the batches being brought forward to the investigator's office, ward or clinic from where they are given to trial subjects. Subjects should return unused supplies or their empty containers.

The auditor should first establish the *modus operandi* at the site from the CRA/monitor, corroborate it through interviews with the investigator and associates and then attempt to substantiate the *modus operandi* further from the paper trail.

#### **8.3.1 Receipt of Investigational Product at the Investigator Site**

Auditors will seldom witness the receipt of supplies at an investigational site, although this can happen if the CRA/monitor attends the audit and combines it with delivery of additional supplies or if additional supplies happen to arrive when an audit is going on. More usually, the task of the

auditor is to reconstruct events from available documentation. With regard to receipt of the investigational product at the investigator site, documentation should include the following:

- A record of drug shipments to the site giving key details such as the quantity delivered, the dates and sometimes the times of day the supplies were received, the name of the courier where one was used and the identity of the person who accepted receipt of the supplies.
- Copies of notifications of receipt for the drug supplies, signed by the principal investigator, an identifiable and authorised delegate, or the hospital pharmacist, and sent back to the sponsor.

### **8.3.2 Storage of the Investigational Product at the Investigator Site**

Whether the supplies are stored in a pharmacy or more locally in the investigator's clinic, ward or office, the auditor should be able to visit the actual location where the supplies are/were stored and to assess the appropriateness of the storage. Typically, supplies might be kept in good conditions such as secure areas, lockable refrigerators, *etc.* – but it is not uncommon for supplies to be stored in less suitable environments such as offices, cupboards, cellars, attic spaces, *etc.* However, all acceptable storage locations of the investigational product need to provide secure and safe storage. The auditor should look for the following conditions:

#### **(i) Physical security**

- the supplies should be in a locked environment
- ideally, people not associated with the trial should not be able to gain access to the supplies, although this is difficult to achieve and often other health care professionals are able to do so
- the supplies should be protected from vermin, but free from contamination with chemical substances such as those sometimes used in rodent bait
- the supplies ought to be reasonably protected from fire
- the supplies ought to be stored off the floor to reduce the risk of damage through floodwater in the event of a burst pipe or actual flooding
- the supplies should be stored so that they cannot become inadvertently mixed with products from other trials

#### **(ii) Environment**

- any temperature or and humidity ranges required for the storage of the supplies must be respected
- the temperature and humidity ranges occurring in the storage facility ought to be recorded and the records, properly annotated and dated, archived
- supplies should not be kept where they may be exposed to solvents or contaminated with other chemicals stored or present nearby
- supplies should be protected from physical vibration and from all risk of accidental damage to the packaging and contents.

### **8.3.3 Prescriptions**

Where a pharmacy is responsible for storing the investigational product it is usual and reasonable to expect a prescription system to be in place for investigational product as it should be for licensed medicines. The auditor should expect to review the appropriate pharmacy records to check those

prescription records indicating the occasions when supplies were removed from the pharmacy. These records ought to indicate the following:

- the identity of the clinical trial subject;
- the date the prescription was signed by the investigator;
- the date the supplies were released from the pharmacy;
- a precise description, including quantities, of what was actually released;
- the pharmacist responsible.

The auditor should be able to correlate releases of supplies with dispensing to clinical trial subjects.

### **8.3.4 Dispensing Investigational Product to Subjects**

While it does happen that individual clinical trial subjects collect their supplies directly from the pharmacy, it is more usual for the investigator to actually dispense the investigational product to the subject. This ought to result in two sets of records, both of which are available to the auditor – a clear reference to what has been dispensed in the subject’s medical notes, and an appropriately completed case record form (CRF). Naturally, the auditor will be concerned to reconcile the information given in these records with the prescriptions to be found within the pharmacy.

Note that it is an express GCP requirement that investigational product is only used in accordance with the trial protocol.

### **8.3.5 Reconciliation and Drug Accountability by the Investigator or Pharmacist**

If the investigator does not wish to conduct supplies accountability personally, he/she may delegate this task to an appropriate individual. Record keeping at the site should be sufficiently comprehensive for the person responsible for supplies accountability, and the auditor, to reconcile all the supplies received from the sponsor through arrival at the site, prescription, dispensing, ingestion, return, and where relevant, destruction.

Where an attempt at this reconciliation reveals that some supplies are not accounted for, it should at least be possible to establish where the records have failed and to know what can be concluded about the fate of the supplies and what cannot be concluded.

### **8.3.6 A Note about Health and Safety**

Research organisations have a moral and legal responsibility to protect their staff and others working for them under contract from risk. In the case of investigational products, this “duty of care” extends to making sure that those transporting or handling the medication are not significantly exposed to it. This can be achieved to a degree through secure packaging but if the packaging becomes damaged or is opened by the clinical trial subject, and during drug accountability checking – especially if individual tablets or capsules are hand-counted – those conducting drug accountability run a small risk of exposure to investigational medicines. It is accepted that the toxic risks will be known from earlier animal and Phase I trials, and that the contamination risk is small and that the exposure could be tiny, but some investigational products contain active molecules presenting a theoretical if not actual risk of toxic or allergic reaction in those exposed. Where a professional pharmacist is assigned responsibility for drug accountability, it is reasonable to expect that all the necessary precautions against exposure to the medicine would be taken. However, this may not be a reasonable expectation for other members of the investigator team, for CRAs/monitors or for auditors, all of whom might also need to count tablets or capsules.

For the safety of all parties involved, it is imperative that all known risks of toxicity associated with ingestion of or contact with investigational supplies are available to those who might be exposed to the supplies through full labelling or information sheets.

The auditor should ask what procedures are in place to minimise these risks and reduce them to an acceptable level and what the process is to report and respond to an actual or possible inadvertent exposure. Neither the auditor nor the CRA/monitor should feel obliged to risk physical contact with an investigational product that is known to have associated risks, or about which too little information has been made available by the sponsor to be reasonably assured about the risk profile.

## **8.4 MONITORING AND AUDITING OF INVESTIGATIONAL PRODUCT BY THE SPONSOR**

This section looks at the respective roles and responsibilities of the sponsor monitor and the professional QA auditor with regard to investigational and comparator supplies.

### **8.4.1 What are the Monitor's Responsibilities in Relation to Supplies on Site?**

The ICH GCP places clear responsibility with the monitor to verify six elements of investigational supplies management at the trial site, and they are summarised here:

- storage conditions are acceptable;
- supplies are not used beyond their shelf life;
- only trial subjects receive investigational products and they receive them in accordance with the trial protocol;
- trial subjects are instructed in how to use, handle, store and return the supplies;
- the receipt, use and return of supplies at the site are adequately controlled and documented;
- unused supplies are disposed off according to prevailing regulations and the sponsor's requirements.

Note that the monitor is not actually required by GCP to conduct drug accountability checks on site – as described earlier this is an investigator's responsibility. Nevertheless, it is common for monitors to conduct drug accountability as a component of source data verification to check that the data supplied by the investigator are reliable. Records of these checks are useful to the auditor both as a double check that supplies are being properly managed at the trial site and as an indicator of investigator diligence at drug accountability.

Note also that the monitor is required by GCP to submit a written report after each trial visit or communication and that these reports should summarise what the monitor checked and found. These reports are available and auditors should always be familiar with them before conducting a site audit. This will enable them to corroborate or challenge the competency of the monitoring and drug accountability processes.

### **8.4.2 What are the Auditor's Responsibilities in Relation to Investigational Supplies?**

The purpose of a sponsor audit is to independently evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements. As is clear from this chapter, this has two components:

- The use of records to verify compliance with GMP, GCP, local laws, regulations, guidelines and codes of conduct, the trial protocol, and sponsor SOPs.
- Verification that the physical facilities in which supplies were stored were appropriate and adequate to assure their integrity for the duration of the trial.

Trial supplies management is always a complex series of processes with multiple components including manufacture, packaging, labelling, storage, transportation, prescription, dispensing and accountability. It is not surprising, therefore, that audit findings are not uncommon and often include the following:

- documentation inadequate to confirm some element of supplies management;
- inadequate storage facilities;
- drug accountability reveals missing supplies that cannot be explained.

Each case will be different and the auditor should assess audit findings against three elements separately:

- Does the finding indicate non-compliance with any known requirement of GCP, the clinical trial protocol, SOPs or the law?
- Does the finding indicate a risk to the integrity of the trial data?
- Does the finding indicate a risk to trial subjects, or to sponsor or investigator team personnel?

All of these are important and need to be carefully evaluated by the sponsor and investigator alike in deciding how to grade and respond to audit findings.

## 8.5 REGULATORY AGENCY INSPECTION

This short section gives some appreciation of the expectations that a sponsor can have about the interest that regulatory authorities usually have in the GCP/GMP interface. The professional QA auditor can prospectively influence the outcome of regulatory inspections by using audits as a means of knowledge feedback to the investigator, monitor and sponsor management alike about the expected and achieved standards of investigational product management. The QA audit department should also be eager to review regulatory inspection findings for insights into how to improve performance.

Regulatory agency GCP inspectors are always interested in clinical trial supplies. They comfortably bridge the GCP/GMP interface, and sponsors should expect to have to provide proof of GMP compliance during manufacture, including the important certificate of analysis, as well as complete documentation on supplies distribution, usage, reconciliation and destruction. Any inability to demonstrate competence in supplies management will be regarded as a serious shortfall, and any proven negligence in this area can expect some resultant regulatory action.

## 8.6 SUMMARY

The GCP/GMP interface is a complex but critical area of clinical research. Auditors can expect documentation relating to supplies to be spread across different departments of sponsor organisations, and across independent organisations (such as couriers) and investigational sites or institutions. Nevertheless, the audit trail must be strong enough to demonstrate compliance with the numerous requirements of GMP, GCP, local regulations, guidelines and codes of conduct, the trial protocol and sponsor SOPs. In addition, the auditor should be ready to physically check the storage facilities used for clinical trial supplies at both the sponsor and the investigator sites.

This chapter has reviewed the provision of investigational product by the trial sponsor, the management of the investigational product at the trial site, the monitoring and auditing of the investigational product by the sponsor and regulatory agency inspections. It has explained the regulatory framework that underpins the GCP/GMP interface and gives practical guidance to auditors to help them work more effectively in this very important area of clinical research.

## REFERENCES

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## CHAPTER 9

# Monitoring and Quality Control

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## 9.1 INTRODUCTION

Since the first International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use in 1991 there have been a myriad of guidelines, revisions to guidelines and regulations laying down the “ground rules” for conducting clinical research. In May 2001, the European Parliament and the Council of the European Union passed a directive<sup>1</sup> which rendered much of what is contained within ICH-Good Clinical Practice (GCP) guidelines<sup>2</sup> enforceable under European law. This Directive was incorporated into the statute books of all of the EU member states by May 2004 when all clinical research conducted within the EU must adhere to a minimum set of standards or run the risk of facing the courts. The pharmaceutical industry has long recognised the need to conduct clinical research to the highest ethical and scientific standards and has therefore developed systems to ensure that clinical research is conducted in accordance with ICH guidelines. Furthermore, since the inception of ICH and the EU Clinical Trials Directive, the Industry is now in a better position than ever to inform Investigators and their research staff of the expectations of clinical research in the 21st Century. However, non-compliance with GCP continues to be a widespread problem.<sup>3–5</sup> Furthermore, much of what might be considered serious non-compliance, for example improperly obtained consent, inclusion of ineligible subjects, study medication incorrectly/inappropriately stored and serious discrepancies between the case report form (CRF) and source data is due to poor training of site personnel leading to poor study conduct at study sites.<sup>4</sup>

The role of the monitor is to review the progress of clinical studies at study sites and ensure, in so far as possible, that (a) the rights and well-being of human subjects are protected, (b) the reported study data are accurate, complete and verifiable from source documents and (c) that the conduct of the study at the study site is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, with the applicable regulatory requirement(s) and with any applicable laws and guidelines.<sup>1</sup> The study monitor is often the first to identify GCP infringements, protocol violations, discrepancies in the data, *etc.* and take action necessary to prevent such problems re-occurring and undermining the quality of the research. Thus study monitoring can be viewed as the “front line” of a quality-control process designed to ensure that clinical research is conducted effectively and to the high standards expected by licensing authorities.

The aim of this chapter is to present a practical guide to quality control at site level and to identify the key areas of the monitoring process, which directly influence research quality.

## 9.2 STUDY PRE-REQUISITES

The setting up and initiation of clinical studies is key to their success and adherence to the ICH guidelines on GCP will normally ensure that a study is placed appropriately and should proceed successfully to completion. However, independent audit findings of 348 study sites in Europe and the United States<sup>6</sup> suggest that the crucial early stages of placement and initiation are often subject to problems that can affect the success of a study. Although much of the “ground work” to a clinical study is often done by study management, with monitors traditionally having little or no involvement until the initiation stage, no discussion of quality control would be complete without addressing placement and initiation procedures.

### 9.2.1 Investigator Selection

Potential investigators may be identified from a number of different sources including:

- discussions at meetings/conferences on the investigator’s research interest;
- literature searches for leading authors in the field (opinion leaders);
- recommendation from professional contacts.

In addition, previous knowledge of an investigator’s work may identify a potentially suitable candidate.

It should be noted that opinion leaders are often sought after as investigators because their name may add credibility to the product under investigation. This does mean, however, that their workload may be too high and their motivation too low for them to be effective investigators. However, the advice and recommendations of an opinion leader may be valuable in identifying qualified but less well-known investigators who have the time and motivation to undertake the study. ICH-GCP mandates that each investigator should be sufficiently qualified and experienced to conduct a study. Furthermore, it is important to establish from the outset that an investigator’s practice is not restricted by any disciplinary action taken by a regulatory and/or professional body, for example Medicines and Health Care Products Regulatory Agency (MHPR), General Medical Council (GMC), *etc.* Once a potential investigator(s) has been identified, an initial assessment of their suitability should be performed. Contact should be made (normally *via* the telephone) to determine the investigators interest and to evaluate, in a very general sense, their capability and resources. One can normally ascertain whether a potential investigator has sufficient interest to conduct a study following a brief discussion of the investigational product, the aims of the study, the study design and outline the expected time frame. Investigators become interested in clinical studies for a myriad of reasons. However, a recent survey of 193 investigators in the Europe and the United States suggests that the level of payment is an increasingly important factor in the decision-making process especially among younger European investigators as compared to their older counterparts.<sup>7</sup> However, factors such as the innovative nature of the drug and the potential to secure future work still rank highly as reasons for participation, and the authors urge caution when dealing with investigators who appear to be pre-occupied with financial matters alone.

Once it has been determined that a potential investigator is interested in conducting a study, a secrecy agreement should be sent for signature. Only on receipt of a signed secrecy agreement should a potential investigator be supplied with confidential study information such as the study protocol and investigator brochure and only at this stage should a site-selection visit be scheduled.

### 9.2.2 The Site-Selection Visit

The site-selection visit is normally the first opportunity for a sponsor/CRO to formally assess a potential investigator and his/her facility. ICH clearly places the onus of responsibility for

investigator selection on the sponsor/CRO. In spite of this, published findings suggest that one in four study sites are initiated apparently without any formal selection procedure.<sup>6</sup>

The first objective of the site-selection visit is to verify the continuing interest of the investigator and to confirm their understanding of their role and responsibilities. It is also important to confirm their qualifications and experience. To this end, a copy of the investigator's curriculum vitae (CV) should be obtained. This should be no more than 12 months old, list their current post and be signed and dated accordingly. In addition to confirming the suitability of the investigator, the suitability of the investigator's staff and facilities should be evaluated. Each member of staff should be identified by name at the site-selection visit and their role in the study determined. Particular attention should be focused on identifying exactly who within a study team will be responsible for the medical care of study subjects and ensuring that this member(s) of the team is suitably qualified for this role. It is worth noting here that it is also important to confirm that each member of the investigator's staff is adequately qualified for their role and therefore signed and dated CVs of relevant personnel should be requested. Attention should be paid to the content and quality of CVs as they frequently go unsigned or lack essential information such as details of usual clinical responsibilities and other clinical-research commitments.<sup>6</sup> It is also worth noting that it is not uncommon for investigators to lack sufficient staff to properly conduct studies and that this may adversely influence data quality.

Even if an investigator has the requisite experience, time and staff to perform a study he/she may not have sufficient patients to meet recruitment targets. Thus, it is important to agree a realistic recruitment target based on information the investigator has about his/her patient population (*e.g.* patient databases) and to request a feasibility study. Also in this respect, it is important to determine if there are any conflicting studies running at the facility, which might hinder recruitment. Unfortunately, confirmation that the investigator has the subject population to perform the study is rarely documented<sup>6</sup> despite this being an important consideration when selecting a study site.

Clearly, any discussion regarding recruitment will involve a review of the key elements of the study protocol such as the inclusion and exclusion criteria. This process of reviewing the protocol is an important part of a site-selection visit. It provides an investigator with the opportunity to raise any queries he/she may have regarding the study, to provide input into the study design and to gain a better understanding of the study requirements. Thus sufficient time should be set aside during the site-selection visit to review critical elements of the protocol such as entry criteria, the scheduling of study visits and key clinical investigations/endpoints.

An inspection of the investigator's facilities is an essential component of the site-selection visit. The investigator should have the appropriate equipment and adequate space (including storage and archiving space) to conduct the study. In addition, calibration and service records should be available for all equipment. Furthermore, the facility should have a suitable locked storage area for study supplies (including CRFs) and have adequate space for monitoring. If the services of a local laboratory are to be used it is also appropriate to inspect these facilities at placement, although survey results have shown that there is rarely any evidence of this.<sup>6</sup> The quality aspects of laboratory conduct in the UK fall under the National External Quality Assessment Scheme (NEQUAS), the details of which exceed the scope of this chapter (see Chapters 12 and 30). However, one should be satisfied that a laboratory is capable of conducting all the required analyses and the following documentation should be requested:

- the Laboratory's procedures and current reference ranges (signed);
- appropriate and applicable certification/accreditation, for example Clinical Pathology Accreditation (CPA);
- copies of protocols for any new analysis specifically commissioned;
- a current signed and dated CV of the Laboratory Manager.

Finally, the administrative and financial aspects of the study should be fully discussed with the investigator, including the ethics committee review process (meeting dates, approval time, *etc.*), regulatory aspects of the study, indemnity requirements and contractual aspects of the study. If the investigator is a member of the responsible ethics committee, written confirmation that he/she did not participate in the review and voting procedure should be requested from the committee.

### 9.2.3 The Initiation Visit

The initiation visit should only be scheduled following a satisfactory assessment at the site-selection visit, once all study supplies are ready for delivery to the investigational site and once the following documentation is in place:

- a letter from the relevant regulatory authority agreeing to the study proceeding;
- a letter from the relevant ethics committee approving the protocol, any protocol amendments, the subject information sheet and consent form and any other documentation, for example letter to primary care physicians, advertising, *etc.*;
- ethics committee composition and constitution (confirming that the approval of the committee is valid);
- signed Indemnity (where applicable);
- written agreement to the protocol and any amendments by the investigator;
- CVs signed and dated (within the last 12 months) for the investigator and his/her staff;
- written agreement to comply with the applicable version of the Declaration of Helsinki;<sup>†</sup>
- a copy of the laboratory certification and reference ranges for all relevant laboratory parameters;
- a clinical study agreement signed and dated by an authorised representative of the sponsor, the institution administering the study and (where applicable) the investigator.

If at the end of the initiation visit any of the above-mentioned documentation is still outstanding, the start of the trial should be delayed. An additional visit may be required depending on the amount of time elapsed between the initiation visit and receipt of the outstanding documentation.

The purpose of the initiation visit is to ensure that the investigator and his/her staff are in a position to start the study and that the study will run according to ICH-GCP and the applicable regulatory requirements. Despite this there are reports of initiation visits taking place before ethics approval and in some cases after subjects have been recruited and issued study medication.<sup>4</sup> The initiation visit can be viewed as “setting the tone” under which the clinical research will be conducted. Thus, inadequate initiation procedures can result in poor quality data and unethical practices, while comprehensive and well thought out initiation procedures are more likely to yield good quality data and lead to safe and valid research.

It is important to ensure that all site staff involved in a study are present at initiation and this should be requested in writing when confirming arrangements for initiation with the investigator. The initiation-visit procedures should cover all aspects of the study and the regulatory and ethical framework under which it is to be conducted. Surprisingly published findings have demonstrated that 36% of initiation visits apparently took place without the investigator being present, while 45% went ahead without the study pharmacist. Furthermore, in 38% of cases there was no documentary evidence that GCP requirements were discussed with the investigator or other

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<sup>†</sup>Paragraph 29 of the current revision of the Declaration of Helsinki (October 2000) states that “extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy”. This has led to some confusion regarding placebo-controlled trials and for this reason there has been some reluctance to adopt the current revision of the Declaration.

research staff.<sup>6</sup> Examples such as these only serve to undermine the overall quality of clinical research and promote unethical and unsafe practices.

The informed-consent process is the ethical cornerstone of any clinical study and the procedures for correctly obtaining written informed consent should be discussed in detail at Initiation. Unfortunately, irregularities such as consent being obtained after the start of study procedures or by non-qualified personnel occur all too frequently in clinical research<sup>4</sup> and may reflect, at least in part, inadequate initiation procedures. Thus, from the outset it is important that the investigator and his/her staff are aware that written consent should be obtained prior to any study-related procedures and following a full and frank discussion with the investigator (or a medically qualified designee). Furthermore, it should be made clear that only subject information sheets and consent forms that have received prior approval from the relevant ethics committee(s) (Chapter 8) should be used in the consent procedure. Published audit findings<sup>3</sup> report that the information sheets and consent forms used at 30% of audited sites failed to adequately inform study subjects of the requirements and implications of the study. Thus, it is important that Subject Information Sheets and Consent Forms are carefully prepared in accordance with applicable guidelines and that the investigator is aware that they should not be informally altered. Revision of the information sheet and consent form will be required should there be any amendment to the final protocol which materially affects subject consent. In this respect the investigator and his/her staff should be made aware that they will need to obtain new consent on the basis of the revised Information leaflet and consent form approved by the appropriate ethics committee(s).

As previously mentioned, it is usual for the protocol (Chapter 2) and any amendments to be discussed at the site-selection visit. However, such discussions are generally preliminary in nature and tend to focus on particular aspects of the study that are pertinent to an investigator's ability to participate, for example key subject entry criteria, visit scheduling requirements, *etc.* Thus, the Initiation visit is normally the first opportunity to review the protocol in detail with all members of the study team. The final protocol should contain all the information required to perform the study. However, the content of clinical study protocols does vary depending on the requirements of sponsor company's SOPs and consequently the following list of discussion points are recommended as a minimum and are by no means exhaustive:

- (i) Background to the investigational product  
Present a background to the product under investigation and familiarise the study personnel with the investigator brochure.
- (ii) Aims and objectives of the study  
Review the aims and objectives of the study and how they relate to the primary and secondary variables.
- (iii) Study design  
Describe the study design (*e.g.* randomised, double-blind, placebo-controlled, cross-over), the reasons for choosing a particular design and control group and the limitations of the chosen design.
- (iv) Subject entry criteria  
Review all inclusion and exclusion criteria.
- (v) Prohibited medication  
Review any prohibited prior and/or concomitant medications and provide the rationale for their exclusion.
- (vi) Study procedures and evaluation schedule  
Describe all efficacy and safety evaluations, the timing of evaluations, sample-handling instructions, including sample storage and dispatch, the use of reference ranges and any specific instructions to be given to study subjects.

- (vii) Medication dosing/device handling instructions and compliance

Describe all investigational products (*i.e.* investigational drug, placebo and/or comparator), the doses to be used in the study, the reasons for using the doses or dose range. Review dosing details such as timing, posture, food or fluid with dose and any restrictions, for example diet, physical activity, *etc.* Review the measures taken to ensure compliance, for example tablet counts, the acceptable range for compliance and describe the possible symptoms of overdose and how this might be treated.
- (viii) Medication storage, accountability and destruction

Describe the specific storage conditions and requirements, the labelling of the investigational product and accountability and destruction procedures.
- (ix) Randomisation and unblinding procedures

Describe the randomisation method, for example random permuted blocks, the method of assigning subjects to treatment groups, for example consecutive allocation, and unblinding procedures (including location of codes, code handling and the circumstances under which unblinding is permissible).
- (x) Safety reporting

Define the terms adverse event (AE), serious adverse event (SAE), adverse drug reaction (ADR) and serious adverse drug reaction (SADR). Review the reporting timelines for SAEs and SADRs and inform the investigator of their responsibility to promptly report SADR information to the appropriate ethics committee.
- (xi) Subject withdrawal criteria

Describe the reasons for discontinuation of subjects from treatment and withdrawal from the study, the nature of any follow-up of discontinued/withdrawn subjects. Discuss any procedures for replacing subjects and the procedures for supplying replacement treatment.
- (xii) Study termination

Review the reasons the study may be terminated before the planned number of subjects has been reached.

Once the study personnel have been thoroughly familiarised with the protocol, the CRF (Chapter 2) and its handling and completion should be discussed. There should be sufficient initial supplies of CRFs at the visit and the monitor should thoroughly review the content of the CRF and instruct all those responsible for entering data into the CRF on the correct procedure for CRF completion. Detailed instructions on study specific aspects of CRF completion should be discussed as well as general instructions regarding CRF correction. In addition, the study personnel should be aware that only the principal investigator is authorised to sign off CRF data and that this should be done on an ongoing basis to facilitate data retrieval. The schedule for CRF retrieval should be discussed and the study personnel informed if this affects the scheduling of study payments. Finally, the study personnel should be reminded of the confidential nature of the CRFs and that these should be securely stored under conditions of limited access.

The ability to verify data entered into the CRFs by direct comparison with source documentation as an important aspect of quality control which provides supporting evidence to a regulatory authority that the data is clean and valid.<sup>6</sup> Thus, the study personnel should appreciate the need to adequately source the data entered into the CRF. In the majority of Phase II–IV studies much of the important background information which determines eligibility, for example demographics, medical history, concomitant medication use, *etc.* will be contained within the subjects medical records which the study monitor will require access to for purposes of source data verification (SDV). The need to access medical records should be discussed at the site-selection visit. However, it is important to confirm and agree on this requirement at initiation. ICH-GCP guidelines recommend that the protocol states which variables entered in the CRF should be derived from source documents and where it is acceptable for the CRF to act as the source, that is data is to be entered



directly into the CRF. Unfortunately, this is not routinely the case, however, to ensure there is no ambiguity regarding source data requirements, these should be discussed with the study personnel at initiation. Clearly source data requirements will differ depending on the complexity of a study and the therapeutic area under study. However, as a general rule, subject identity, demographics, eligibility, the primary efficacy and safety variables, adverse events and concomitant medications should be verifiable from primary sources.

In addition to holding and maintaining CRFs and source documents, the investigator will hold much of the documentation pertaining to the study including regulatory approval letters, ethics approval letters, all study agreements (including the protocol and any amendments), *etc.* This is normally collated in a file (normally referred to as an investigator file or the site file) which the investigator is expected to maintain and which the monitor will be expected to review from on a regular basis throughout the study. A review of the investigator file should be undertaken at the initiation visit and the presence of all the documentation required to start the trial should be confirmed.

While there are an appreciable number of investigators who have a good understanding of ICH-GCP, equally there are a number who, for reasons of naivety or entrenchment, fail to appreciate the ethical and scientific framework to which they are expected to adhere. Consequently, GCP non-compliance is widespread and therefore, it is vital to allocate sufficient time during the initiation visit to discuss and familiarise the study personnel with the principles of ICH-GCP and the particular aspects that apply to the investigator, that is ICH topic E6. Although it is likely that many of the aspects of ICH-GCP that are applicable to the investigator, for example adequacy of resources, informed consent, compliance with the protocol, safety reporting, *etc.* will have already been covered, it is important to emphasise and reinforce these aspects of the study, as well as others such as the investigator's responsibility to communicate with and reporting to the applicable ethics committee(s), in the context of ICH-GCP.

Finally, as some time will have elapsed since the site-selection visit, it is important to confirm the continuing suitability of the investigator's facility. Thus the study personnel and equipment to be used in the trial should be re-evaluated at initiation. In the case of the latter, any outstanding maintenance and calibration records should be obtained.

## 9.3 MONITORING

### 9.3.1 Training the Monitor

The responsibility for implementing and monitoring quality systems lies with the sponsor. Therefore, only individuals who have received adequate training should be assume the role of monitor. The vast majority of monitors either have a degree in a life science or a nursing qualification, which, although providing firm foundations on which to build the skills required to monitor clinical studies, do not prepare individuals for the monitoring role.

In essence, ICH-GCP requires the monitor to be suitably qualified to supervise the overall conduct of a clinical study and ensure that it is conducted, recorded and reported in accordance with the protocol, protocol amendments, standard operating procedures (SOPs), GCP and the applicable regulatory requirements.<sup>1</sup> Furthermore, the onus of responsibility for training lies with the sponsor, that is sponsors should not expect monitors to be responsible for that which they have not been trained. Therefore, training should be formalised within a company (in line with SOPs) to ensure that future monitors are suitably prepared for their role and experienced monitors are fully aware of company procedures and do not have to rely solely on previous experience. The following topics may be included in the training of monitors:

- principles of ICH-GCP
- informed consent

- recruitment
- adverse events and safety reporting
- study medication and drug accountability
- source data verification
- research methods (including protocols)
- data capture and data management (including CRFs, data queries, *etc.*)
- biological sample handling
- report writing
- communication skills.

In addition, in order that inexperienced monitors gain a full understanding of their roles and responsibilities, it is often appropriate for newly appointed monitors to accompany more experienced colleagues on site visits before embarking on solo monitoring visits of their own.

### 9.3.2 Frequency of Monitoring Visits

The ICH-GCP guidelines stipulate that a monitoring visit is required before, during and after the study. The frequency of visits often depends on the development phase, study complexity and recruitment rate. It is recommended that the first monitoring visit should occur immediately after the enrolment of the first subject at a study site (or certainly within 2 weeks of first enrolment) or within 6 weeks of initiation if no subjects have been enrolled. The scheduling of the first monitoring visit is important as it is the first opportunity to assess study conduct and identify at an early stage any areas of concern, for example recruitment, consent irregularities, protocol violations, *etc.*

*Phase I studies* are, as a general rule, monitored every 2–4 weeks. However, more frequent visits are often indicated, for example early Phase I studies in which the toxicity of a drug has yet to be determined in man. In addition, the monitor is often required to verify that the study drug is being administered correctly and in accordance with the protocol and that any deviations from the correct dosing procedure are documented appropriately. Therefore, it is not uncommon for monitors to be present at the first dosing session and may be expected to be present at all dosing sessions.

*Phase II and Phase IIIa studies* tend to require less-intense monitoring than Phase I, with visits typically occurring at least every 4–6 weeks. Again, circumstances may dictate more frequent visits, for example rapid subject recruitment, GCP non-compliance, *etc.*

*Phase IIIb and Phase IV studies* are typically monitored at 8–12 weekly intervals, although again circumstances may dictate more frequent visits.

In addition to on-site monitoring, the progress of a study should be monitored by frequent telephone calls. The content of these calls should be recorded in writing.

### 9.3.3 Setting Objectives for Monitoring Visits

It is important that a monitor does not embark on a site visit “blind”. Therefore, each monitoring visit should be preceded by a review of the study-site status and any issues that may need to be addressed. Thereafter, in order to ensure efficient monitoring, the monitor should develop a clear list of objectives for the visit. Failure to adequately prepare for a visit will result in inefficient and unfocused monitoring that is reactive rather than proactive. The following is a standard list of routine objectives for a periodic visit:

- (i) check subject consent has been given as per requirements (ICH-GCP and the Declaration of Helsinki);
- (ii) check compliance with subject entry criteria as specified in the protocol;

- (iii) verify adherence to protocol procedures, including laboratory evaluations;
- (iv) verify accuracy and completeness of recorded data in the CRF by comparing with the original clinic or hospital records (SDV); where discrepancies are found, to arrange for their correction and to advise study-site personnel to ensure the problem does not recur. Source data should always be compared to CRF data and not *vice versa*, as it is important to identify data omitted from the CRF.

In addition the following items are typically checked during a periodic site visit:

- (i) Subject identification

Subjects should be clearly and correctly identified in the CRF by any study-specific subject number, initials and randomisation number (where applicable). In addition, all subjects should be readily identifiable from a subject identification log.
- (ii) Consent forms

Original signed and dated consent forms should be available for all subjects entered into the study. The monitor should check that the correct version of the subject information sheet and consent form is in use and that all forms have been personally signed and dated by the subject, the consenting physician and any others involved in the consent process, for example parents/guardians, witnesses, *etc.* In addition, the monitor should check that all signatures bear the same date, and that this does not post-date any study-related procedure. Furthermore, it is recommended that, where possible, the monitor check that the subject's signature is genuine. This is commonly done by comparing the signature on the consent form with other forms that bear the subject's signature, for example consent for a surgical procedure.
- (iii) Subject inclusion/exclusion criteria

Subject eligibility should be checked against all study inclusion and exclusion criteria and verified against information in the medical notes. Typically, the following details will need to be checked when determining eligibility:

  - demographic data (age, gender, ethnicity);
  - medical history (prior and inter-current medical conditions);
  - prior and concomitant medication.

Any instances of non-compliance must be raised with the investigator and sponsor and an action plan detailing the handling of inappropriately entered subjects agreed upon. In the majority of cases the most appropriate course of action is to immediately withdraw the subject from the study. However, it is not unknown for sponsors to allow ineligible subjects to continue, although this course of action should be discouraged as it may encourage further protocol violation.
- (iv) Recruitment and subject progress

Recruitment rates should be closely monitored and the monitor should keep a record of subject progress. If recruitment is less than optimal, the reasons should be determined and the monitor should suggest ways in which it can be improved. Poor recruitment can be a consequence of lack of investigator motivation, focus or time or the result of competing studies.
- (v) Key efficacy variables

The primary and secondary key efficacy variables should be checked for accuracy and completeness. Any missed or mistimed evaluations should be discussed with the investigator and an explanation sought.
- (vi) Medication accountability

The monitor should periodically conduct an inventory of the study medication and ensure that the supply, storage, disposition, compliance and return of the study

medication is fully documented and that any discrepancies are quickly reconciled to ensure medication accountability records are up to date and accurate. The monitor will also be responsible for ensuring that any returned and/or unused medication is removed from site for eventual destruction.

(vii) Randomisation

The monitor should check (where applicable) that group allocation of the study medication is being performed in accordance with the protocol and that investigators making assessments are being kept truly blind to the nature of the treatment.

Furthermore, where randomisation codes are stored at the study site, the monitor should routinely check their integrity and ensure that they remain in a secure but readily accessible location. If a code is opened, for example in the case of a medical emergency, the monitor should check that the code envelope has been signed and dated by the investigator at the time of opening and the reason for opening the code has been fully documented.

(viii) Adverse events

The monitor should continuously review adverse events (including any clinically significant laboratory abnormalities) and maintain a record of AEs occurring during a study. Should a SAE be noted, the monitor must ensure this is correctly recorded on SAE Form and in the CRF and is reported to the sponsor in writing in a timely manner (usually within 24 h of first knowledge). Unreported SAEs that are discovered during a monitoring visit should be reported to the sponsor immediately. Furthermore, the monitor should ensure that the investigator forwards a written report to the sponsor before the end of the day.

(ix) Concomitant medication

Concurrent medication should be routinely reviewed by the monitor. Any change to existing medication (whether the complete cessation of a drug or a change in dose, route or frequency) should be recorded in the CRF, as should any newly introduced medication.

(x) Study supplies

The monitor should ensure that there are sufficient in-date supplies of study medication at the site. Where any re-labelling of the study medication is required, for example in the case of a re-test that extends the expiry date, the monitor should check that the re-labelling has been performed correctly and that it still conforms to GMP requirements.

(xi) Biological samples and assay results

The monitor should check that any biological samples are collected, stored and dispatched for analysis as per protocol and/or laboratory instructions and that there is adequate documentation to confirm this. Furthermore, the monitor should ensure that the results of any analyses are accurately reported either in the CRF or on laboratory reports and, where necessary, are being reviewed and interpreted by the investigator or an appropriately qualified designee.

(xii) Continued acceptability of facilities and personnel

The monitor should assess the continued suitability of the study personnel and facilities throughout the study. Should the monitor have concerns about the adequacy of the facilities or the suitability of any of the study personnel, these concerns should be raised with the investigator and the sponsor who should reach mutual agreement on a plan of corrective action. The monitor will then be required to check that that this action is being instituted. In addition, any newly appointed study personnel should provide the monitor with a current signed and dated CV that demonstrates that they are adequately qualified and experienced for their role and responsibilities in the study as designated by the investigator on the signature log. Finally the monitor will be responsible for ensuring that any personnel newly appointed to the study are fully initiated into the study.

(xiii) Documentation

The monitor should regularly check that the investigator file is being maintained correctly and where deficiencies are noted, take action to bring the documentation up-to-date. Correspondence should be frequently reviewed as should the subject identification log.

### 9.3.4 Source Data Verification

Source data and the process of SDV are an essential part of clinical research. Essentially source data is the original documentation or recording of study-specific information relating to a study subject and can take the form of paper documents, for example subjects medical notes, laboratory reports, diary cards, dispensing records, *etc.* or as photographic or electronic records, for example X-rays, microfiches, videotape, *etc.* An important role of the monitor is to verify, by direct comparison with source data, the accuracy of some if not all the data entered into the CRFs. This validation procedure (termed SDV) ensures the integrity of the data and therefore forms a crucial part of the on-site QC process and from a regulatory perspective provides evidence that the data is true and accurate when submitting for a product licence.

Source data forms an important part of the audit trail and as such all source documents must be retained for inspection at audit. Theoretically, all data entered into the CRF should be verifiable from source. However, this is not always practicable and there may be occasions where data are entered directly into the CRF, for example serial vital-signs measurements in a Phase I study, thus making the CRF the source document for that data. In this case, ICH-GCP, Section 6.4, makes it absolutely clear that if the CRF is to be accepted as the source data for specific items then these items must be defined in advance and preferably in the study protocol itself.

The CRF should only constitute the source in exceptional circumstances where it is not practical to transcribe data from source documents. Therefore, in reality most study data will be subject to SDV and it is routine to perform SDV on the following data:

- Demographics
- Visit dates
- Medical history
- Prior and concomitant medications
- Results of laboratory investigations
- Key safety and efficacy endpoints
- Vital signs
- Adverse events.

### 9.3.5 Frequently Reported Problems

In 1996, Good Clinical Research Practices published a summary of audit findings from 226 GCP studies<sup>3</sup> and some of the most frequently reported problems highlighted in their report are presented in Table 1 (clearly, there are multiple observations for each site). What is apparent from these results is that without exception they all could be overcome by instituting quality systems at the site level. All too often monitors spend far too much time performing data checks and SDV, which although they have an important QC role, can distract the monitor from broader and perhaps more crucial issues such as ethical conduct, safety reporting. The monitor should be viewed by the sponsor and the study-site team as a partner in the clinical study and as such should spend a proportion of his/her time focusing on and developing GCP-compliant quality systems at study sites, which will ultimately benefit data quality and integrity and study conduct.

**Table 1** *A summary of commonly reported audit findings from GCP study sites*

<i>Finding</i>	<i>% of sites (n = 226)</i>
Significant discrepancies between source notes and the CRF data	35
Adverse events not reported (or inadequately reported)	14
Informed consent obtained after the start of the study procedures	37
Informed consent taken by persons other than the authorised investigator(s)	50
Subject's GP not informed about study participation	71
Details of study treatment (start/finish dates, dose, regimen, <i>etc.</i> ) not entered in subject's source notes	57
No record of dispensing of study medication maintained at the site	27
Dispensing records only partly complete	48
No evidence that local ethics committee were notified of serious adverse events	81

*Note:* Based upon data from Bohaychuk and Ball (1996).<sup>3</sup>

### 9.3.6 Documenting the Monitoring Visit

The evidence of the quality of monitoring is provided in the monitoring report, which, in the first instance, serves as a means of feeding-back information regarding the status and conduct of a study at a particular study site to study management. However, the monitoring report also forms a vital part of the audit trail, which allows an auditor to re-construct the course of events of a study thus facilitating the audit process. One criticism levelled by auditors is that monitoring reports are all too often inadequate, lacking the level of detail needed to complete the audit trail.<sup>8,9</sup> Furthermore, this criticism is generally not aimed at individual monitors, but rather the constraints of the system a monitor must work within.<sup>9</sup> Thus, the effectiveness of the monitoring report in providing evidence of the quality of monitoring is highly systems dependent. A survey of documentation from 384 study sites in the United States<sup>9</sup> revealed that in only 69% of cases monitoring reports were available for all monitoring visits, thus making it impossible to complete the audit trail. Furthermore, the same survey highlighted some glaring omissions, with only 41% of reports adequately documenting compliance with visit requirements and only 43% documenting that drug expiry date had been checked. This data suggests that much improvement is required in monitoring documentation.

### 9.3.7 Components of an Effective Monitoring Report

Regulatory authorities generally take the stance that “if its not documented, it didn't happen”. Therefore, the type of information and level of detail contained within a monitoring report is of utmost importance when it comes to audit inspection. Furthermore, if as is suggested above, the quality of monitoring is highly dependent on the systems available, it is clear that particular attention should be focused on what the key components of an effective report should be. It is recommended that the following points are fully and accurately documented in a monitoring report:

- date of a visit;
- all study personnel present;
- all activities performed during a visit (*e.g.* CRF review, SDV, data collection);
- any adverse findings (*e.g.* consent irregularities, data inconsistencies, protocol violations) and any action taken, or required, to resolve them;
- the ethics status of the study;
- the recruitment status of subjects;
- the safety status of subjects;
- randomisation procedures;



- changes in study personnel and facilities;
- management of study supplies;
- correctness of laboratory/clinical procedures;
- maintenance of study records.

It is important that a monitoring report is not merely a checklist, which the monitor may use to direct his/her activities at the site, rather it should allow for sufficient narrative and encourage the monitor to document in detail all activities that were actually performed.

## 9.4 STUDY SITE CLOSURE

The most common reason for closing a study site is the successful completion of all clinical work. However, there are a number of other reasons for closing a site. A site may be prematurely closed should a study achieve its global recruitment target. Alternatively, slow subject recruitment may also necessitate site closure. Furthermore, a decision to terminate the study may be made in the light of newly emerging drug safety and/or tolerability issues that would necessitate site closure.

A decision to close a study site may be made by the sponsor, investigator, ethics committee or regulatory body. However, irrespective of who or what instigates site closure, a standard procedure should be adopted by the monitor to ensure that all issues are resolved prior to termination. What follows is a description of a recommended procedure for study-site closure, which should ensure that any outstanding issues are identified and resolved and that all study data and documentation is complete, up-to-date and stored for appropriate time periods as required by ICH-GCP and regulatory bodies.

### 9.4.1 Pre-Closure Visit Procedures

Prior to the final visit to a study site, the monitor should review all previous monitoring reports to identify any outstanding issues that will need to be addressed before or during the site closure. He/she should also review the sponsor's and investigator's files to identify any gaps in the documentation. It is important that outstanding issues or requirements for documentation are identified prior to the visit, as it is unlikely that the investigator will have the motivation to chase, supply and file documentation after site closure. Finally, the monitor may be required to ensure that all necessary payments have been made to the site and that there are no outstanding financial issues that might prevent site closure.

### 9.4.2 Final Visit to the Study Site

The overall aim of the final study visit is to leave no unresolved matters except those that can easily be handled remotely, for example data-query resolution. The site-closure visit may be an extended monitoring visit. However, the monitor must in addition confirm the following points:

- all data have been correctly completed, monitored, verified against source data and collected;
- all data queries produced to date have been correctly completed and collected;
- all adverse events have been fully and accurately recorded and adequately followed up;
- all drug supplies have been fully accounted for and that any remaining supplies have been dispatched for eventual destruction;
- all other study supplies (unused case-report forms, extra protocols, unused specimen containers, *etc.*) have been accounted for and removed from site;
- all randomisation codes, if held at site, are present and ready for collection and, where a code has been broken, the reason(s) for breaking a code has been fully and correctly documented;
- the investigator file is complete and up-to-date and that any deficiencies can be rectified;



- all samples collected during the study have been shipped from study site to an appropriate destination.

The investigator and key personnel, for example research nurse, pharmacist, should be present at the closure visit in order to (a) help the monitor resolve any queries and (b) raise any queries that may arise during closure. In addition, the monitor should discuss the following points with the investigator during the site-closure visit:

- final reporting responsibilities to the ethics committee;
- the final study report and publication of study results;
- the possibility that a representative of the sponsor may return with any queries that arise during statistical analysis or report writing and agree follow-up procedures;
- archiving responsibility of study documentation as per ICH-GCP and applicable regulatory guidelines. This point should also be discussed with the pharmacist to clarify their archiving responsibilities;
- to advise that site may be required to participate in an audit at any time by the sponsor, regulatory or other authorised bodies.

### 9.4.3 Documenting Site Closure

Following a site-closure visit, the monitor should prepare a site-closure report. This should document in detail all the procedures and discussion points listed above and any action points requiring follow up. Assuming all the objectives of the site-closure visit have been achieved and the visit has been suitably documented, the investigator can formally be informed of site closure. This is most commonly done *via* a letter to the investigator thanking them for their study participation and documenting in writing the conditions under which the study has been concluded and the responsibilities of the investigator following site closure.

## 9.5 CONCLUSIONS

The monitor has a crucial role ensuring the smooth initiation, conduct and conclusion of a clinical study. Furthermore, the monitor's role in ensuring that on-site quality systems are instituted and maintained, that data is checked and validated and that study personnel are regularly updated and trained is a vital part of a QC process. This ultimately aims to ensure that the study is conducted according to the requirements of ICH-GCP and regulatory bodies and that study data are clean and accurate and subjects are adequately protected.

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## CHAPTER 10

# Phase I Healthy Volunteers Studies

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### 10.1 GENERAL NATURE OF PHASE I STUDIES

The development of new medicines entails a phased exposure to the drug, firstly in a small group of healthy volunteers and progressively in larger population of patients, thus,

- *Phase I* studies involve the first or early administration of the medicine in humans. The aims are to establish safety and tolerability or to assess pharmacokinetics and pharmacodynamics in healthy volunteers.
- *Phase II* studies usually involve first exposure of the product to patients with the target disease.
- *Phase III* studies involve larger patient population and are designed to confirm efficacy and safety in patients, often using a comparative product and/or sometimes a placebo.
- *Phase IV* studies are larger comparative studies post-marketing surveillance, *e.g.* of safety or to detect previously unreported adverse events that have a low incidence rate.

Phase I studies (or bioequivalence and bioavailability studies) have many characteristics that are different from those of later phase studies, resulting in specific requirements for the Quality Assurance (QA) systems, as described in Table 1.

Owing to these differences, the ideal skill profile of a QA auditor for Phase I units is likely to be slightly different than for later phase units. This should be considered at the recruitment stage, when it must be clear exactly which competencies are sought.

### 10.2 RECRUITMENT OF QUALITY ASSURANCE STAFF

#### 10.2.1 Scientific Skills

The common image of a QA person is someone who has good attention to detail and the methodical thought process of a scientist. These are important qualities, and will help ensure that audits are carried out in an efficient way by someone who is suited to analysis of systems and who therefore is likely to enjoy the work more. However, there are other qualities that are also essential in a Phase I auditor.

#### 10.2.2 Flexibility

Since Phase I units can be multi-functional (*i.e.* bioanalysis, pharmacokinetics, clinical pathology potentially also on site), the type of audits conducted can be quite diverse and technically

**Table 1** *Comparison of healthy volunteer studies with later phase studies*

<i>Difference</i>	<i>Consequence</i>	<i>Solution/Actions</i>
The timescale for start-up, execution and reporting of a Phase I study is generally much shorter than that for later phase studies. There is often urgency to start human exposure to a drug in the shortest possible time from the completion of the required pre-clinical package	This means that QA audit schedules must be flexible to cope with study schedule changes at short notice, and audits may have to be conducted within a short space of time to catch a procedure in progress or satisfy deadlines	Maintain constant awareness of study schedules and developments by frequent liaison with key staff. Build in flexibility of structure, and ensure that auditors are cross-trained if possible, so that resources can be diverted quickly from one area of audit to another
Many principal investigators in Phase I studies are either employees of the sponsoring company (for in-house Phase I units) or full-time employees of commercial organisations that are reliant on fees from sponsors for their income	Availability of principal investigators at a particular time is potentially better than in later phase trials	Take advantage of this situation by including the investigator in discussion of audit findings
In many late-phase trials, a patient is being treated with a medicine, or comparator, or placebo where there is expectation of benefit in health. Many early-phase studies are conducted in people where there is no benefit expected. The nature of the incentive for many subjects in Phase I studies is financial rather than medical	Subjects may be tempted to ignore restrictions, which although may be necessary for scientific delivery of the protocol, may not seem to be important to the subject	Increased focus on volunteer compliance during procedures audits. Examination of arrangements to maximise volunteer compliance (e.g. physical security, supervision, fines, etc.) during system audits
In late-phase clinical trials, the dose or doses are specified in advance and hence can be packed appropriately, well in advance of the study. In many Phase I studies, flexible dosing over a wide range may be required via protocol amendments during the study	Pharmacy facilities must be adequately resourced at all times in terms of qualified staff and appropriate facilities, and staff on shifts should communicate efficiently at changeover	Since safety is the primary consideration in clinical trials, focus on this area is necessary for each individual study. A pre-study risk assessment based on degree of complexity of pharmacy procedures may be useful to decide if this area requires particular scrutiny by the QA auditor
The Phase I facility is smaller but often is multi-functional and so comprises many different departments	A wide range of quality issues may occur in departments that can be effectively almost independent of each other	Recruit QA staff who are willing to learn and capable of acquiring a diverse range of soft and hard skills. Design training program accordingly
In Phase I, the sponsor and the investigator work for different organisations, so that relations between the two parties are more formal	Clear definition of responsibility for the various aspects of the quality of the study can be lacking	The contract should define exactly what duties are being performed and by whom to clarify the relationship
In Phase I studies, it is often acceptable for both monitors and QA personnel to be present in the wards to observe the live phase of the trial. This is not usually the case for later phase trials involving patients	QA procedures audits may be carried out, examining aspects of GCP compliance such as protocol and SOP compliance by actual observation of raw data being collected	Plan procedures inspections on a study-specific or process basis and scheduling by reference to the study timetable

challenging. The new recruit then should be potentially able to audit data in a field that he is not qualified in. In fact, many of the principles of auditing are independent of the type of data inspected. Training in specialist areas can certainly be given, often by in-house managers, to ensure that the QA auditor understands, on a basic level, the procedures involved. However, a willingness and ability to learn about new scientific fields is necessary.

### **10.2.3 Communication Skills**

In a multi-functional environment, the QA auditor will liaise with people drawn from a variety of disciplines. Therefore, the QA auditor should be confident speaking to a wide range of people – from nurses to bioanalytical laboratory managers.

### **10.2.4 Recruitment**

When searching for a new QA auditor, it is important that the correct questions are asked at the interview. Scientific skills can be explored by asking technical questions about work, academic courses or research the candidate has conducted. The ability to tackle new tasks is a more difficult quality to assess, but the candidate's reaction when a large technical report is presented to them as an example of the type of information involved during a report audit can be enlightening! Do not forget to explain about the training that would be involved, though, otherwise you may discourage a potentially excellent recruit! Interpersonal skills can often be readily determined at interview: explore if the candidate can talk intelligently by asking open-ended questions, preferably about both familiar and more challenging subjects.

After recruitment of a new QA auditor, if an opportunity arises, it is useful to involve the auditor as an observer in a study-site audit, such as an assessment of a Clinical Research Organisation's (CRO) facility by a new sponsor before the work is formally placed. The new recruit can learn about the systems that are essential to support a clinical trial, perhaps as a precursor to performing study audits on trial procedures and trial data.

## **10.3 AUDITS OF INVESTIGATOR SITES BY THE SPONSOR**

These audits examine in detail, for the first time in the sponsor's experience, the investigator's systems in order to ensure that an infrastructure exists that will consistently generate work to the required regulatory standards. Phase I CROs offer a wide range of services, and so a careful coordination of the audit is necessary to ensure that the auditor obtains all the information required. The audit may be conducted by sponsor QA personnel or contracted to independent QA auditors, and involves a visit to the facility, often hosted by the investigational facility's QA manager. The audits can vary in style from a good-natured discussion to formal interviews with staff followed by a rigorous examination of records. Owing to the limited time allotted to audits and the complex nature of Phase I units, some auditors select limited areas for inspection, which can give an incomplete picture of the facility. There are normally one to six auditors and duration is usually 1–2 days. It is also not uncommon to combine these audits with an initial discussion of potential study-specific issues with operational staff, in which case project managers from both parties would be involved.

The initial contact should make clear the scope and timing of the audit. An agenda should be prepared which will form the basis for planning the audit. The host should consult the managers of sections that will be audited to decide audit dates and then construct a schedule that includes a meeting between each section manager and the auditors, followed by examination of documents. This strategy ensures that the auditor receives accurate information and most managers are prepared to explain their own systems. Remember that, except for matters directly relating to his own area of responsibility, the acting host is coordinating the audit rather than the sole auditee.

Sometimes among auditees, there is a fear of misrepresenting the company. This fear lessens with experience and can be mollified by some sympathetic coaching. Staff should be polite and open at all times, answering questions accurately and succinctly. If systems are criticised unfairly then they have a right to be assertive, while all the time remaining calmly receptive to innovative ideas from the auditors, which may aid the continuous improvement process.

This audit schedule should be circulated to all involved for feedback, and if managers cannot attend then delegation to an acting deputy is required. Prior to the audit, documents may be requested from the auditors and these may be usefully supplied, with the exception of any documents such as unique in-house developed methods that may be regarded as confidential. Any reasonable requests (*e.g.* standard operating procedure (SOP) indices) should be met, but requests for large volumes of documents (*e.g.* copies of many SOPs) are usually discouraged since this means uncontrolled release of business details. All documents will be available for on-site inspection instead.

On the day, adherence to the timelines of the schedule should be diligently managed by the host since there is a tendency to overrun timeslots. This can lead to section managers becoming unavailable to meet with the auditors. A close-out meeting at the end of the audit is normally carried out to ensure that audit findings are clear. Reponse to the written audit report, performed by coordination of feedback from individual section managers, is usually required within a defined time period.

Phase I facilities with a large client base often receive large number of client audits, and although demanding in resource these audits must be recognised as a source of useful advice that can facilitate important quality improvements. Where conflicting advice is given from different sponsors, a compromise system that satisfies all parties may be the best approach. The option of not acting upon a finding should also be considered, particularly if you can convincingly defend the system against the finding.

At some stage, usually after the facility has been approved, the protocol and case report forms (CRFs) are finalised. This process is worth examination by the QA auditor, since this is the foundation of the study, though there is some debate whether this should be a formal audit or not.

#### **10.4 CONTROL OF PROTOCOL AND CASE REPORT FORM QUALITY**

Phase I studies may progress from concept to study start in a few weeks, making control of critical document such as the protocol and CRF very important. Protocols may be authored by the sponsor or investigator, and may be considerably more complicated than later phase protocols. Significant amendments are more likely since study design may have to be modified as new data become available, resulting in fundamental changes in procedures. CRFs may be produced at the last minute, perhaps a few days before the study starts. All this puts pressure on the document control system, which can be alleviated by a QA team prepared to be involved outside the scope of normal QA audit activities.

A standard template is useful for protocols written by the investigator to ensure that the document is comprehensive and easy to use by the operational staff, who become accustomed to finding information from a document in a familiar format. Sponsor-derived protocols may be either adapted to this format, or (more likely) imposed on the investigator. These protocols can be more difficult to interpret, especially if they do not contain a clear, complete, chronologically ordered schedule of study events. Close teamwork between sponsor and investigator is the ideal solution, in order to produce a protocol that is to an acceptable format but also can be used as a clear, user-friendly reference document.

Prior to study commencement, the QA auditor will read through the protocol and CRF, *e.g.* in preparation for a procedures audit, familiarising himself with procedures involved and identifying areas potentially prone to error. This can be an ideal opportunity to check for internal



inconsistencies and compare protocol with CRF. QA comments on the protocol and CRF can be fed back formally as part of the quality control (QC) process, though this involvement in QC can be interpreted as a loss of QA independence from operational processes. Another way to return comments is by informal discussion with study staff before study start to resolve queries. Either way, it is the duty of the conscientious QA auditor to communicate any comments about protocol or CRF before the study starts. Certainly, it is best to propose preventative actions than wait until they happen and then report them as findings!

Typical findings during the protocol/CRF examination are listed below:

- The tabulated summary of the study schedule does not match the procedures in the text
- There are ambiguous passages that require clarification
- Procedures are not in chronological order and there is no clear schedule
- There are other inconsistencies in different parts of the text
- All protocol amendments are not available
- It is unclear whether amendments overwrite previous ones
- Procedures in the CRF and protocol are not always consistent
- The CRF is not very user-friendly and the staff members need to be familiar with it before the start of the study.

Since events move very quickly, there is often little time to perform an examination of final versions of protocols and CRFs. If possible, it is a good idea for the QA auditor to request being copied in on earlier drafts of these documents, for familiarisation only, if time allows, resulting in faster appraisal of final versions.

A large section of the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines is devoted to approval of the protocol, consent form and information for volunteers by an independent ethics committee (IEC), so this is an area that also may benefit from scrutiny by the QA unit.

## 10.5 INDEPENDENT ETHICS COMMITTEE ACTIVITIES

All ethics committees must be established and recognised in accordance with the regulations, namely Statutory Instrument 2004 No. 1031, Sections 5–16 and Schedule 2 (and 1a amendment Statutory Instrument 2006 No. 1928). Required SOPs are detailed in Schedule 2 Section 6, and documents requested to accompany an application are described in Schedule 3.

QA audit is recommended to ensure that these independent bodies are properly set up and work to accepted standards. On a systems audit basis, the following procedures should be documented by the committee.

- Composition
- Timeliness of study review
- Initial and continuing trial review process
- Approval and feedback process
- Treatment of protocol deviations and new information
- Notification of serious or unexpected adverse drug reactions (ADRs)
- Appeal procedures
- Record retention
- Suitability to review Phase I protocols.

These documents should be managed by the IEC themselves, being careful that full independence of the committee is maintained.

Inspection of ethics committees is appearing less and less on the QA agenda, since these national regulations should effectively police IEC operations. Certainly for in-house QA units any audit which inevitably will result in recommendations, could be regarded as interference with a body which essentially must remain independent.

An examination of all the documents associated with a particular submission, from protocols considered to minutes of the meeting and documented actions undertaken as a result, is a useful exercise that will pick up significant operational issues.

On a study-specific basis, the procedures audit is usually the tool to confirm that the protocol, any amendments, consent form and information for volunteers have been approved by the IEC. There should be a clear record of all proceedings involving the IEC in the investigator's study file.

The consent process in Phase I studies is different in nature to that involved in patient studies and brings its own issues for the QA auditor.

## 10.6 INFORMED CONSENT

Although there is some element of altruism and curiosity in people who are volunteering for Phase I studies, the financial incentive is often a significant motive. On one hand, this is more transparent than the situation of some later phase studies where there may be some subtle coercion by physician investigators for grateful patients to take part in clinical trials. On the other, it can lead to unreasonable pressure. From the quality point of view, it is essential that systems for calculating remuneration are transparent so that there is no element of payment for risk (only inconvenience and discomfort) to avoid undue pressure on subjects.

The process for obtaining consent is a process that is invariably of great interest to all parties: regulators, sponsors and investigators. It follows that this must be an area in which standards are high and therefore subject to careful QA inspection. The fundamental questions that a QA auditor might ask are as follows:

- How is the payment for studies calculated?
- What payment is made if subjects leave the study?
- What study information is provided for volunteers?
- How much time do volunteers have to read this information?
- When can subjects leave a study?
- What information is provided on the consent form?
- Who signs and witnesses the consent form?
- What is your policy for using company employees as volunteers?
- How do you check if the volunteer understands the information provided?
- Who approves the consent form?
- What is the procedure for revision of the consent form?
- What sort of technical language is used in the consent form?
- Does the content satisfy Section 4.8.10 of the ICH-GCP guidelines?

A logical payment structure is essential, since volunteers will often weigh up the pros and cons of payment *vs.* inconvenience. Studies that they consider to be poorly paid will be difficult to recruit. Over payment however, especially for studies involving a potentially increased incidence of ADRs, raises ethical issues, and so a balance must be struck in the payment formula to ensure optimum, ethically sound recruitment.

There will be technical data available from animal studies and perhaps previous studies in man. Relevant parts of this should be included in the information provided for volunteers, but in layman's terms so that it is as clear as possible. Oversimplification is always a risk here, and IEC advice is normally used to determine general style.

Use of company employees or relatives is generally discouraged because of the potential for coercion, even though one could argue that the willingness of company employees to participate gives other volunteers confidence in the control of safety.

After consent to participation in the study and the restrictions it imposes, one would hope that the volunteer honours this agreement as far as reasonably possible. A Phase I unit must take measures to ensure the study subjects, usually mobile, healthy and young people, are properly managed while they are confined in a facility that they will probably find rather boring.

## 10.7 VOLUNTEER CONTROL

Given that there will always be a limited capability of keeping them amused during quiet times of the study, facilities for recreation are desirable, which may include television, video, books and games.

In addition to keeping them happy between study activities, general house rules and study-specific coaching must ensure that they behave appropriately and cooperate with the investigator's staff. Non-compliance with study procedures might include, for example, not attending for blood sampling or clinical measurements in the ward, thus compromising study power. This can be observed at a QA procedures audit and volunteer control assessed.

Security must prevent unwanted guests entering the building, or volunteers accessing areas they have no need to be in. Also, some areas will only be accessible to certain staff, *e.g.* the pharmacy and archive. Experiences that demonstrate security lapses must be followed up to so that the situation can be remedied. Generally, entry and exit of volunteers to and from the building should be predictable, *i.e.* there should be a standard access route and no "secret" back doors out of view of study staff. Volunteer movements should be observed during procedures audits as an indicator of study control.

Food-effect studies involving defined diets demand a control of food/drinks available at the facility and coming into the facility. Volunteers are asked only to bring in essential personal belongings and both people and belongings may be searched. Kitchens should be restricted areas, accessible only to catering staff. Non-compliances relating to the consumption of food are very difficult to detect, so prevention is the best strategy. In these types of studies, the importance of detailed recording of food provided, consumed and left should be targeted during procedures audits, since during most other studies food consumption is not so important and staff can forget to focus sufficiently on this critical area.

It is obviously important that volunteers are able to tolerate their stay and do not feel incarcerated. However, the building must be secure enough to maximise compliance and restrict volunteers to "safe" zones. Exploration during system audits designed to examine security will highlight areas of concern.

We have already mentioned procedures audits in Phase I facilities, the aim of which is to observe first-hand the clinical procedures undertaken and the recording of the raw data as it happens. The content of these audits merits more detailed discussion.

## 10.8 IN-LIFE PROCEDURES AUDITS

These audits are not usually done in later phase clinical trials, since understandably hospital facilities are often not receptive to the disturbance of their patients.

The audits are normally conducted on a day when activity in the ward is most intensive, since this is the time when systems are most pressured. The first-hand witnessing of study procedures involved in the audit is an invaluable help in understanding how studies are run and potential hidden risks to data integrity. Later audits, which only inspect data (as discussed in Chapter 6), cannot ensure that the records have been collected according to protocol and good scientific practice.

A protocol summary, comprising a chronological list of study procedures on the day, is a useful aid to auditing. The auditor can usefully check some aspects of study preparation such as sample tube labelling on the day before the study starts, and should arrive relatively early on the first day of the study to catch early procedures like equipment set up or drug preparation. Typical audit checkpoints are listed below, with at least SOP and protocol adherence being considered for each point.

- Sample container labelling
- Use of the current ethics committee approved protocol
- Informed consent records
- Drug preparation by pharmacy
- Pre-dose procedures
- Drug dispensing
- Collection of data from clinical procedures
- Recording of data
- Study management
- Safety monitoring
- Volunteer management
- Sample treatment and processing
- Sample storage and transfer

Some QA units target only certain areas for each study, after a risk analysis has identified those areas, but conduct the full procedures audit at defined intervals, *e.g.* every five studies.

Care should be taken not to help in the conduct of the study unless in an emergency, since this compromises independence. Some auditors find this difficult, especially during intensive procedures, but if the study staff members are aware of the auditor's role, they are less likely to try and involve him. Occasionally talking to staff during the study is fine, but take care not to disturb their concentration or you might have to cite yourself as the cause of an audit finding!

Where several critical procedures take place simultaneously, the procedures audit may be conducted over several phases or more than one auditor may be used.

Always remember that the point of the exercise is to observe a sample of study procedures, focussing in on the more critical areas. Some audit findings may be addressed immediately but others will need further discussion at meetings, perhaps involving a variety of people, in order to ensure that the causes of problems are tackled.

Since procedures audits directly observe the collection of raw data, they can be a useful tool in discouraging fraud. The CROs are expected to have SOPs for the detection and prevention of fraud, and incidences of fraud have resulted in regulatory changes designed to make fraud more difficult.

## 10.9 FRAUD AND SOURCE DATA VERIFICATION

Since Phase I clinical trials do not involve the treatment of disease, it could be argued that the nature of the work is more commercially orientated than in the hospital surroundings of later phase trials. This usually results in a high standard of professionalism in the conduct and reporting of the trial, but systems must be in place to ensure that there is a high probability that any incidences of fraud are detected.

The most useful detection tool, which forms the backbone of any QA audit anyway, is audit trail tracking. The audit trail comprises the trail of data that starts at source data through various data transformations to the final report.

Probably the first question mark should be attached to the original data; does it come from real subjects? There have been cases where data such as electrocardiograms (ECGs) from one subject were regenerated a number of times and attributed to other non-existent subjects. Incidences such as these should be relatively easy to spot, but what if apparently perfectly reasonable data such as blood pressures are fabricated for each subject? Tracing a sample of subject names and dates of birth back to reliable medical records is the obvious test of whether trial subjects are genuine. In Phase I trials, checking of CRFs against the medical history obtained from interview and the volunteer's general practitioner (GP) is part of the source data verification process. It must be clear what actually constitutes the source data, which generally can be defined as the original recording. If study measurements are written directly into the CRFs, then this is source data itself. If worksheets are used and the data transcribed across to CRFs, the worksheets are source data and the CRFs must be 100% verified against them by some QC process. The QA audit will include a verification that any necessary QC processes have been carried out.

Simple statistical parameters such as standard deviation can be used to determine the likelihood of a particular spread of results coming from a normal population, and screening of the range of clinical recordings by a physician can be useful if foul play is suspected.

Confirmation of the integrity of the data trail is also used as a standard QA audit tool to confirm the validity of final reported data. Any corruption somewhere between raw and final data can be discovered by validation of the transformation of a sample of raw data to the final reported data.

It is actually very difficult to generate false clinical trials data without leaving some evidence. It is standard practice during QA audit to examine cross-consistency of information such as dates of events, and fraud has often historically been detected by observation of inconsistencies. Where there is a reason to suspect fraud however, it is also advisable to be vigilant beyond the usual bounds of the standard audit and investigate thoroughly any aberrant data to decide if a deliberate or accidental process was at work.

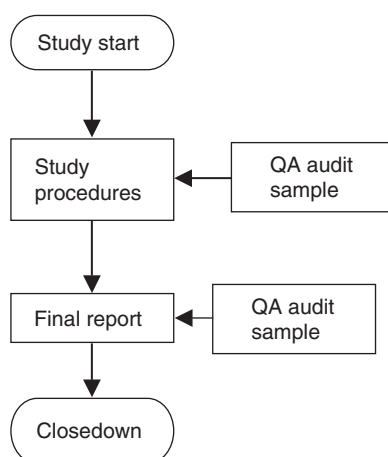
Many regulatory developments, such as the good practice standards we work today, have their origins in the prevention of fraud. A development applicable to Phase I bioequivalence studies requiring United States Food and Drug Authority (US FDA) scrutiny is the requirement for investigators to retain, for 5 years, a sample of both formulations amounting to five times of that required for release testing. This is the consequence of a study where the two formulations tested were actually identical assuring that testing showed bioequivalence. As a result, FDA now requires the facility for confirmatory analysis of the formulations involved, hence the necessity for the retention period.

For the detection and investigation of fraud, it is vital that the QA auditor involved has a high level of independence from the process involved, so that there is no vested interest. This is also generally important during routine, pro-active QA audits, since to assess the performance of a system it is advantageous not to work within the system.

## 10.10 QUALITY ASSURANCE INDEPENDENCE

Maintaining the independence of the QA unit is vital to its proper functioning, but this can be a special type of challenge in the relatively small Phase I facility. The QA unit cannot be directly involved in operations that it itself audits, though obviously catalysing system improvements brought about by audits or from other sources is very much part of their role.

If we imagine the study as a flow of events, the QA auditor is not actually within this flow process since this would be a QC role that is inconsistent with performance of independent QA audits. The QA auditor samples the process from outside as an observer, reporting his findings to management in order to encourage improvements. Figure 1 illustrates the nature of the QA auditor's involvement during study-specific audits. During procedures audits, for example, where study procedures are being observed, any active involvement to help things go smoothly can disturb what we are



**Figure 1** *Position of the quality assurance auditor during study audits*

trying to measure. Involvement in tasks such as 100% checking of CRF completeness should not be a function of the QA auditor, and indeed it is unlikely that the QA unit will have the resources to perform in-process QC such as this anyway.

In a Phase I unit, it is vital to define clearly the role of QA auditor and to resist the inevitable pressure to regularly perform routine QC tasks. This role may be usefully described in QA job descriptions and policy documents, approved by senior management, covering the sampling nature of audits with a direct reporting line to management that maintains the independence of the QA unit from day-to-day operations.

### 10.11 SUMMARY

While there is similarity between activities undertaken during Phase I studies and those occurring during a later phase, where differences occur, it is important that these differences are reflected in the audits performed by the QA departments of both the sponsor and the investigator. A successful QA department supporting Phase I studies is usually one that can work flexibly with timelines and across a variety of disciplines, adapting quickly to new challenges in a task-oriented manner and able to reconcile the different quality standards in operation.

## CHAPTER 11

# Clinical Laboratories

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## 11.1 INTRODUCTION

### 11.1.1 Background

A clinical laboratory or, as is more commonly known in the UK, a medical laboratory or clinical pathology laboratory, is one that deals with the theoretical and technical aspects of biochemistry, haematology, endocrinology, bacteriology, immunology, virology, mycology, parasitology and cellular pathology (histology and cytology) as they pertain to the prevention or diagnosis of disease and the care of patients and welfare of the community. They may be used for the analysis of clinical or animal specimens in the form of blood, serum, plasma, urine, faeces or other excreted, extracted or swabbed biological samples derived from the progression of all phases of clinical trials or non-clinical studies.

Clinical laboratories may be clinical pathology departments of local National Health Service (NHS) trusts, private pathology businesses specialising in providing clinical pathology services to the private health care sector, or specialist analytical laboratories providing clinical trials services to the pharmaceutical industry.

The type of study undertaken by clinical laboratories will generally involve only the analysis of specimens and reporting of results directly to the sponsor or their agent and may not even include the laboratory receiving a copy of the study protocol. On the other hand, a specialist analytical or clinical research type of laboratory may be involved in contracted regulated studies and may require a study director or principal investigator, study plan and final report.

### 11.1.2 Scope

The main purpose of this chapter is to introduce clinical laboratories to the quality professional generally involved in clinical trials. It describes and illustrates the structure, procedures, accreditations, compliances and quality systems of laboratories. The term “clinical laboratory” is used to describe a medical or clinical pathology laboratory for the purpose of consistency.

Included is a practical guide to inspecting clinical laboratories. This will be of use to those actively involved in selecting, using or monitoring such laboratories. In addition, there is a section concerning the implementation of quality systems in clinical laboratories. This is felt to be of importance due to the introduction in 2003 of revised standards for clinical laboratories by Clinical Pathology Accreditation (CPA) UK Ltd. This is a major step forward in clinical laboratory accreditation in the UK. For the first time quality standards specifically designed for clinical pathology have been introduced, which make the implementation and maintenance of a quality management system (QMS) essential.



Clinical laboratories exist generally in order to provide clinical pathology services to NHS trusts or the private health care sector with clinical trial work being a small, but nonetheless important area of their workload. With this in mind, a typical laboratory involved in the analysis of clinical trials samples may have a number of different standards to work with different priorities and different specimen handling procedures, analytical procedures and reporting structures.

### 11.1.3 Legislation

At present, there is no mandatory accreditation required in the UK for clinical laboratories *not* involved in clinical trials. Blood transfusion is governed by the Blood Safety and Quality (amendment) Regulation 2006 No. 2013 and follows Good Manufacturing Practice (GMP). Laboratories may seek accreditation or compliance under the auspices of the College of American Pathologists (CAP), CPA and United Kingdom Accreditation Service (UKAS) to satisfy customer and business requirements or adhere to a voluntary scheme such as Good Clinical Laboratory Practice (GCLP). Laboratories involved in pre-clinical studies would be members of the Good Laboratory Practice (GLP) compliance programme (Statutory Instrument 1999 No. 3106, The Good Laboratory Practice Regulations 1999), and those performing clinical trials would be subject to the ICH Guideline for Good Clinical Practice (Statutory Instrument 2004 No. 1031, The Medicines for Human Use (Clinical Trials) Regulations 2004).

Standards in laboratories can differ widely. Some laboratories may have no formal quality system consistent with an accrediting body. It may be found that some laboratories provide an accurate and secure service but have little appreciation for the level of documentation and record keeping required for the purposes of clinical trials. This situation, however, has changed rapidly with the introduction of the latest CPA standards and clinical trials legislation. In the past, due to the high cost of participating in accreditation schemes, some laboratories chose to “work to the relevant standards” without formal participation.

When selecting, using or inspecting a laboratory, these issues must be taken into account and the number of laboratories from which to choose may be limited due to the constraints of location, price or the expertise available.

### 11.1.4 Responsibilities

The scientist involved in clinical trials has the responsibility to ensure the safety and well-being of all those involved in the trial procedures and to conduct the trial procedures to the highest standards thereby ensuring the maximum safety and benefit to the recipients of the final pharmaceutical product.

## 11.2 CLINICAL LABORATORIES IN THE UK

### 11.2.1 Types of Clinical Laboratories

In the UK clinical laboratories generally fall into two main categories: those within the public sector and those administered by private businesses. Public sector laboratories are the clinical pathology departments of NHS trust hospitals. The disciplines found within the clinical pathology department may include biochemistry, haematology, blood transfusion, endocrinology, microbiology (which may consist of bacteriology, immunology, virology, mycology and parasitology) and cellular pathology (histology and cytology). Phase I studies (Chapter 10) are often performed in hospital laboratories monitoring a drug's effect on the body (pharmacodynamics) by measuring routine clinical pathology parameters before and after administration. A private laboratory may be the clinical pathology department of a private hospital, a clinical pathology business existing in

isolation from a hospital or an analytical laboratory specialising in analyses for clinical trials and other pharmaceutical studies and may be part of a contract research organisation (CRO). The latter type of laboratory may have divisions within its organisation such as a bioanalytical section to provide the expertise for developing specialised tests in animals for non-clinical pharmacodynamics and investigations into the body's effect on the chemical substance (pharmokinetic studies) and a section for providing routine screening and specialised tests in humans for clinical trials. Table 1 shows the typical tests performed by a clinical laboratory involved in subject screening and pharmacodynamic studies for a Phase I clinical trial. The specimens for these analyses may be whole blood, serum, plasma and urine that are often sent to the laboratory by courier or by post.

*11.2.1.1 Public Sector Clinical Laboratories.* Clinical pathology may be taken as a subsection of the pathology department of a hospital.

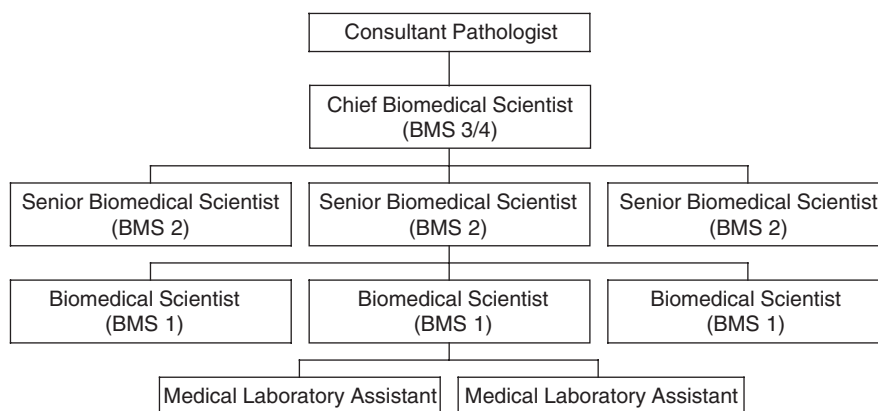
In an NHS laboratory with CPA accreditation, professional direction of the disciplines is provided by consultant pathologists or clinical scientists of equivalent status as dictated by the trust management. There may be an overall Director of Pathology, covering all disciplines. In the United Kingdom, competence of consultant pathologists is usually demonstrated by membership of the Royal College of Pathologists or its equivalent.

Figure 1 shows an organisational diagram for a discipline in an NHS trust hospital clinical laboratory.

In order to practise within the NHS, the laboratory staff must be registered with the Health Professions Council (HPC). This is known as HPC registration, formerly known as state registration. The HPC, formerly known as the Council for Professions Supplementary to Medicine (CPSM), is an independent, UK-wide regulatory body responsible for setting and maintaining standards of professional training and development, performance and conduct of the 12 health care professions that it regulates. There are two types of clinical laboratory workers registered with the HPC: Biomedical Scientists (BMS) and Clinical Scientists. A BMS is a scientist who analyses

**Table 1** *Typical clinical pathology tests performed by a clinical laboratory involved in a Phase I clinical trial*

<i>Biochemistry</i>	<i>Haematology</i>	<i>Microbiology</i>	<i>Drugs of abuse screening</i>
Alanine aminotransferase (ALT)	Differential leucocyte count	Urine microscopy	Amphetamines
Albumin	Haematocrit		Barbiturates
Alkaline phosphatase	Mean cell haemoglobin (MCH)		Benzodiazepines
Aspartate aminotransferase (AST)	Mean cell haemoglobin concentration (MCHC)		Cannabinoids
Bilirubin	Mean cell volume		Cocaine
Calcium	Red cell count (RBC)		Codeine
Cholesterol	White cell count (WBC)		Dihydrocodeine
Creatinine			Ephedrine
Gamma glutamyl transpeptidase (GGT)			MDMA (ecstasy)
Globulin			Methadone
Glucose			Methamphetamines
Total protein			Morphine
Triglycerides			
Urate			
Urea			



**Figure 1** Organisational diagram for an NHS trust hospital clinical pathology laboratory

specimens from patients to provide accurate scientific data to help doctors diagnose and treat diseases. A Clinical Scientist oversees the provision of specialist tests for the diagnosis and management of diseases. Clinical Scientists advise doctors on the use of tests and interpretation of data and perform scientific research to understand disease processes and devise new therapies. The professional bodies associated with BMSs and Clinical Scientists are the Institute of Biomedical Science and Association of Clinical Scientists, respectively.

Also, in the laboratory, there may be Medical Laboratory Assistants (MLAs) whose function is to carry out, under supervision by qualified staff, routine tasks in a laboratory that do not require the skill and training of a state registered BMS.

**11.2.1.2 Private Sector Clinical Laboratories.** Private laboratories are diverse in their services. They may offer a wide range of tests and services to the medical and pharmaceutical sectors or they may be solely concerned with analysing a small range of clinically significant parameters for monitoring the effects of specific drugs on a small section of the population.

These laboratories fall into two main types: those which closely resemble the clinical pathology laboratory of an NHS trust hospital and those with a predominantly analytical chemistry background, maybe offering clinical research services.

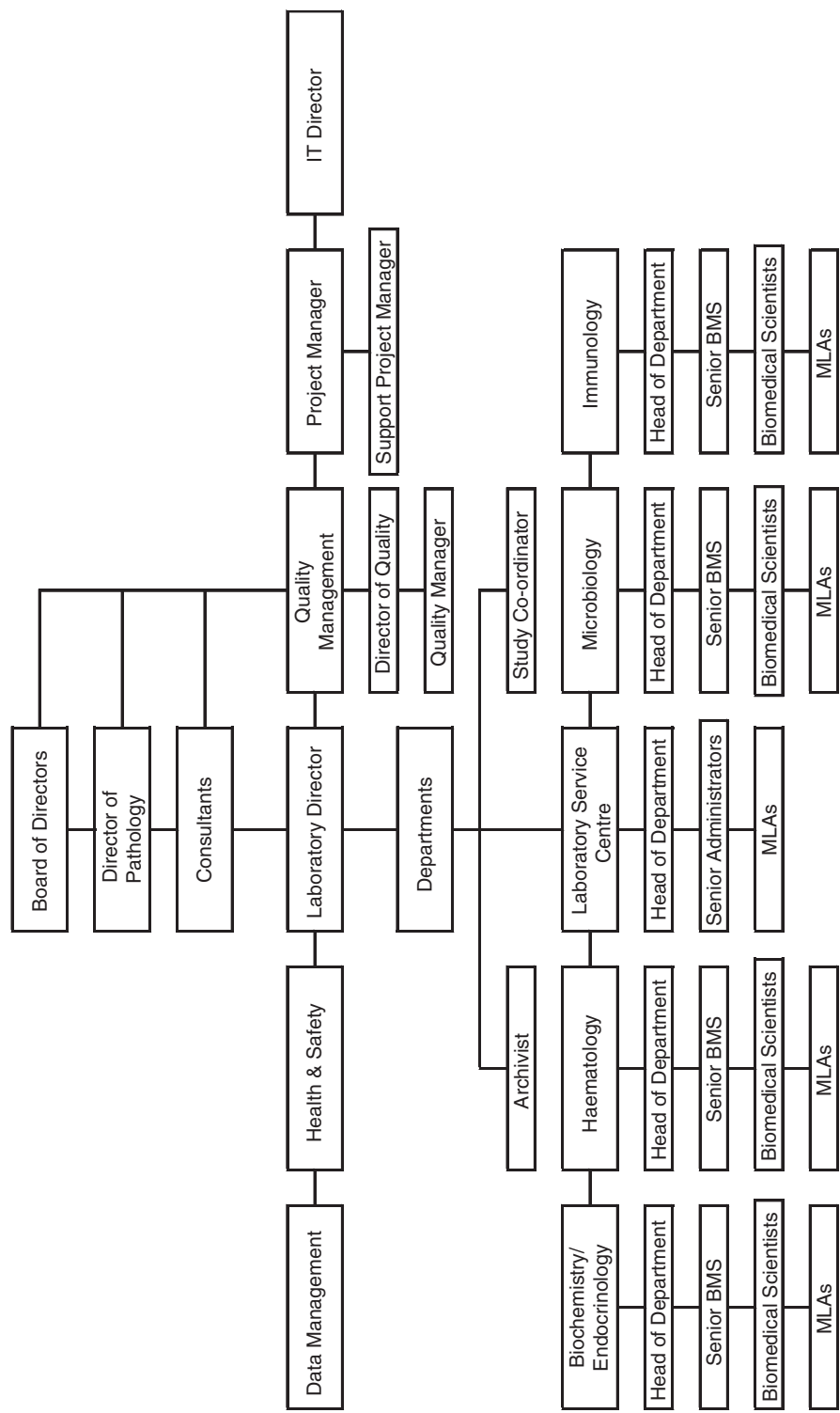
Private laboratories are businesses and have management structures that encompass the whole business. This may lead to a general, company-wide approach to implementing philosophies such as quality. Figure 2 shows the organisational diagram of a typical private clinical pathology laboratory.

A laboratory staff working in the private sector tends to be qualified as either a BMS or an analytical chemist or equivalent. The BMSs are HPC registered as in the NHS and analysts are usually graduates in chemistry or even holders of higher degrees in analytical chemistry or related subjects; even analysts with membership of the Royal Society of Chemistry (MRSC) and Chartered Chemist (CChem) status are common.

## 11.3 ACCREDITATION IN THE CLINICAL LABORATORY

### 11.3.1 Introduction

The CPA defines accreditation as “The procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks”. By working with a



**Figure 2** Organisational diagram for a private clinical pathology laboratory

defined series of standards and having this independently confirmed, an accredited laboratory is able to offer reassurance of compliance to its users.

### **11.3.2 A Brief History of Accreditation for Clinical Laboratories in the UK**

Accreditation for clinical laboratories in the UK is a fairly recent phenomenon. Before 1992 laboratories engaged in analyses for clinical trials had a limited choice from GLP (before the statutory instrument), NAMAS (National Accreditation of Measurement and Sampling, now UKAS), CAP or BS5750 (British Standard for a QMS later to be revised as ISO 9000:1994 series of standards). The BS5750 offered a QMS for general business manufacturing and service industries that was not specific to laboratory analyses. The CAP was specific to clinical pathology but was little known to laboratories in the UK, although it was understood internationally by sponsors and CROs. The NAMAS provided accreditation for specific tests or calibrations that were traceable to national or international standards (e.g. British Standards Institute) and therefore could be costly and time consuming for a laboratory with a large repertoire of routine tests. The NAMAS tended to be chosen (as is UKAS today) for laboratories engaged in drugs of abuse testing, water testing and microbiological examination of foods. This led some laboratories to look to membership of the GLP compliance programme as a solution. At least two private laboratories were enrolled into the GLP compliance programme in the early 1990s. This appeared to be a turning point for laboratory accreditation in the UK. The CPA arrived in 1992, the product of a joint venture between the Royal College of Pathologists and the Association of Clinical Pathologists, its main objectives being to introduce quality standards to the NHS clinical pathology laboratory and associated services such as external quality assessment (EQA) scheme (proficiency testing) providers. The CPA launched its standards after careful study of accreditation schemes for pathology services in North America and Australia and feasibility studies in the UK. CPA gained momentum during the 1990s and largely became the preferred standard among public and private clinical laboratories. This was to be further enhanced with the publication in early 2001 of “Standards for the Medical Laboratory” by CPA (UK) Ltd. These standards were the result of a review of existing standards in response to the first drafts of a new international standard, ISO 15189 “Quality Management in the Medical Laboratory”, which was circulated in 1996. In February 2002, CPA (UK) Ltd. entered into a partnership with UKAS with the objective of delivering national and international recognition of CPA accreditation activities. This was further strengthened in 2004 by the signing of a formal agreement on the accreditation of medical laboratories by the two organisations to the ISO 15189, which was published in 2003. The likelihood of accreditation for medical laboratories becoming mandatory in the near future has been discussed at recent CPA meetings. Should this happen then the CPA–UKAS liaison could provide the appropriate vehicle for realisation. ISO 15189, as the internationally recognised standard governing medical laboratories, may become the preferred accreditation system in the future. With the implementation of the EU Clinical Trials Directive and subsequently of UK Statutory Instrument, GCLP was envisaged in March 2003 and published by the British Association for Research Quality Assurance (BARQA) for laboratories involved in the analysis of clinical trials samples to enable compliance with GCP guidelines.

### **11.3.3 Requirements for Compliance**

There are different requirements for accreditation and compliance in the clinical laboratory depending on the type of work the laboratory undertakes. In the following section the application, definitions and requirements for compliance and other details are discussed for the main standards of CAP, CPA, GCP, GCLP and GLP in relation to clinical and analytical laboratories. The compliance with any standards would indicate a well-managed laboratory with an established Quality Assurance (QA) programme that would be suitable to carry out clinical trials in line with GCP guidelines.

### 11.3.3.1 College of American Pathologists

**11.3.3.1.1 Application.** Hospital and non-hospital clinical laboratories in the private sectors and CROs with laboratory facilities would consider CAP accreditation suitable. The main advantage of CAP accreditation is that it is internationally recognised. Pharmaceutical companies are global organisations and it therefore makes sense to apply a uniform, internationally known standard to participating laboratories.

**11.3.3.1.2 Definition.** The CAP provides the following definition of its accreditation programme: “The goal of the CAP Laboratory Accreditation Program is to improve the quality of clinical laboratory services through voluntary participation, professional peer review, education and compliance with established performance standards. Upon successful completion of the inspection process, the laboratory is awarded CAP accreditation and becomes part of an exclusive group of more than 6,000 laboratories worldwide that have met the highest standards of excellence”. Laboratory accreditation is mandatory in North America.

**11.3.3.1.3 Requirements.** In order to gain accreditation a laboratory has to comply with a series standards under four main headings:

Standard I	Director: qualifications, responsibilities and role Delegation of responsibilities Consulting pathologist
Standard II	Physical facilities and safety
Standard III	Quality control and performance improvement Quality control Proficiency testing (EQA in United Kingdom) Instrument maintenance Quality improvement/performance improvement
Standard IV	Inspection requirements

Laboratories are accredited for a 2-year cycle, but they conduct a self-inspection every year.

### 11.3.3.2 Clinical Pathology Accreditation

**11.3.3.2.1 Application.** Hospital and non-hospital clinical laboratories in both public and private sectors and CROs with laboratory facilities would consider CPA accreditation suitable. Clinical trials mostly involving routine testing could be carried out under CPA but not non-clinical studies. CPA accreditation is awarded for individual disciplines within an organisation: biochemistry, haematology, microbiology, immunology, cytology and cellular pathology.

**11.3.3.2.2 Definition.** The CPA document “Standards for the Medical Laboratory”, version 1.03, November 2004 specifies the requirements for the management of a medical laboratory. It covers the organisation and quality management, the resources and the evaluation and QA activities required to ensure that pre-examination, examination and post-examination activities of the laboratory are conducted in such a manner that they meet the needs and requirement of the users. It is intended that compliance with these CPA standards would signify the ability of a laboratory, by appropriate certification or accreditation procedures, to comply with the essential criteria and international standards (e.g. ISO 15189) as referred to in the standards.

**11.3.3.2.3 Requirements.** In order to gain accreditation and comply with these standards, a laboratory has to satisfy a series of eight main standards:

- A Organisation and Quality Management System (QMS)
- B Personnel
- C Premises and environment
- D Equipment, information systems and reagents
- E Pre-examination process
- F Examination process
- G The post-examination phase
- H Evaluation and QA

Accreditation is valid for a 4-year period. However, there is a requirement for annual re-registration, an interim surveillance inspection and a self-declaration form stating continuing compliance with the standards.

### *11.3.3.3 Good Clinical Laboratory Practice*

**11.3.3.3.1 Application.** GCLP is applicable to any organisation that analyses samples generated during the conduct of a clinical trial. These might include pharmaceutical company laboratories, CROs, central laboratories, pharmacogenetic laboratories, hospital laboratories, clinics, investigator sites and analytical laboratories.

There are commercial companies that offer inspection and accreditation services for GCLP but generally the standards are applied and monitored voluntarily. The standards are based on the laboratory requirements of the GLP regulations.

**11.3.3.3.2 Definition.** GCLP is intended to provide a framework to those organisations and individuals that undertake analyses of samples from clinical trials on the facilities, systems and procedures that should be present to ensure the reliability, quality and integrity of the work and results generated during their contribution to a clinical trial.

**11.3.3.3.3 Requirements.** There are 13 main standards:

- Organisation and personnel
- Facilities
- Equipment, materials and reagents
- Standard operating procedures (SOPs)
- Planning of the work
- Sub-contracting
- Trial materials
- Conduct of the work
- Reporting results
- Quality control
- Quality audit
- Storage and retention of records
- Confidentiality.

Accreditation offered by a provider requires annual accreditation for the first 3 years of membership of the scheme. After 3 years on the scheme, a laboratory will only require assessment once every 2 years.



For hospital laboratories most of the above-mentioned requirements are provided by the CPA standards if implemented fully.

#### *11.3.3.4 Good Clinical Practice*

**11.3.3.4.1 Application.** Hospital and non-hospital clinical laboratories in both the public and private sectors, analytical and clinical research laboratories and CROs with laboratory facilities engaged in the provision of analytical services for clinical studies would be subject to the application of GCP principles.

GCP compliance is not an accreditation scheme for which laboratories can subscribe. However, compliance is now a matter of law in the UK. – The European Union Clinical Trials Directive 2001/20/EC was drawn up into the UK legislation in May 2004 (see Section 1.3). In anticipation of the implementation of legislation relating to clinical trials, the Medicines and Healthcare Products Regulatory Authority (MHRA) – formerly the Medical Control Agency (MCA) – which is responsible for the assessment of all requests for authorisations to market drugs in the UK, established a GCP compliance unit in 1996.

**11.3.3.4.2 Definition.** The ICH Topic E6 “Guideline for Good Clinical Practice” (CPMP/ICH/135/95) (1997) defines GCP as “A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected”.

The principles established in the guidelines may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

**11.3.3.4.3 Requirements.** GCP provides an essential framework within which clinical trials are conducted. Clinical laboratories are part of the process and as such must adhere to the overall standards but are not specifically covered.

Within the ICH Topic E6 “Guidelines for Good Clinical Practice” (CPMP/ICH/135/95) (1997), the GCP principle of Section 2.12 is that which is most pertinent to services offered by a clinical laboratory. This may be taken to mean that a laboratory should have procedures (SOPs) for its systems (analyses or tests) and ensure the quality of every aspect of it (have a QMS).

Furthermore, the “Essential Documents for the Conduct of a Clinical Trial” of the guidelines show that the requirements for medical laboratories are normal ranges (reference ranges) for the procedures to be included in the protocol and evidence of the laboratory’s competence in terms of certification, accreditation, established quality control (QC), EQA or other validation.

One change brought about by the transposition of the Directive 2001/20/EC into national legislation was the introduction of mandatory inspections to assess compliance with GCP (and GMP) at sites of sponsors, CROs, academic research organisations, investigational trial sites, clinical laboratories, GCP archives and other facilities involved in clinical trial research of medicinal products.

The MHRA is considering how often NHS sites will need to be inspected. Sponsors are also obliged to audit a laboratory to evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements.

#### *11.3.3.5 Good Laboratory Practice*

**11.3.3.5.1 Application.** The GLP regulations require that any test facility that conducts, or intends to conduct a regulatory study, must be a member, or prospective member, of the UK GLP compliance programme. A regulatory study may be taken as a non-clinical experiment or set of experiments in which examinations are performed under laboratory or environmental conditions in

order to obtain data for regulatory authorities on a substance's properties and safety with respect to human health, animal health or environment.

Rather than a clinical laboratory, this type of study would more likely be conducted within a specialist research or clinical research establishment, perhaps also offering routine pathology screening among its repertoire of analytical procedures.

**11.3.3.5.2 Definition.** The MHRA's definition is "Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, cosmetics, food and feed additives and contaminants, novel foods and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments".

**11.3.3.5.3 Requirements.** The principles of GLP cover 10 parts:

Part I	Test facility organisation and personnel
Part II	Quality assurance programme
Part III	Facilities
Part IV	Apparatus, materials and reagents
Part V	Test systems
Part VI	Test and reference items
Part VII	Standard operating procedures
Part VIII	Performance of the regulatory study
Part IX	Reporting of regulatory study results
Part X	Storage and retention of records and materials

A laboratory may be contracted to provide a portion of the analytical services required for a study. The Guide to the UK GLP Regulations is quite specific about the control and monitoring of contracted-out work. In order to claim GLP compliance for a study, contracted-out work has to be judged to be performed to GLP principles either by a laboratory within the UK GLP compliance programme or as an extension of the sponsoring test facility's GLP and QA system.

Laboratories in the GLP compliance programme are inspected every 2 years by the MHRA.

## 11.4 QUALITY ASSURANCE IN THE CLINICAL LABORATORY

### 11.4.1 Introduction

A clinical or analytical laboratory wishing to perform non-clinical and/or clinical studies may find itself having to adhere to a number of the standards discussed here. On the other hand, a sponsor or CRA may wish to contract out a study to a suitable laboratory that, although having an excellent quality of analysis and service, has no formal QA programme. In both cases, the adoption of a formal QA programme ensures the necessary management direction and monitoring to enable accreditation or adherence to compliance programmes. The QA function is a part of the overall quality objectives of the laboratory or business that are established, performed and monitored by a QMS. Interpretation of the requirements of the different standards can be a major problem for clinical laboratories looking for work in clinical trials. Table 2 gives some essential QA definitions for a QMS. With these in mind and the elements of QA required for CAP, CPA, GCLP, GCP and

**Table 2** *Quality definitions for CAP, CPA, GCP and GLP*

<i>Definition</i>	<i>CAP</i>	<i>CPA</i>	<i>GCP</i>	<i>GLP</i>	<i>Suggested definition for clinical laboratories</i>
Quality Assurance (QA)			All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirement (s)	A defined system, including personnel, which is independent of how a study is conducted and is designed to assure test facility management of compliance with the principles of GLP	The use of monitoring techniques, including inspections and audits, to promote confidence in laboratory results; to assure the quality of the data generated and to ensure compliance with quality standards such as CAP, CPA, GLP and GCP
Quality improvements	In laboratory medicine, this is the process of assuring that all pathology services involved in the delivery of patient care have been accomplished in a manner appropriate to maintain excellence in medical care	Part of a QMS focused on continually increasing effectiveness and efficiency			
Quality management system (QMS)		System to establish a quality policy and the quality objectives and to achieve those objectives			
Quality control (QC)			The operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled		The use of techniques to reduce discord and discrepancy in results of measurement of the same quantity in the same material
External quality assessment (EQA)					EQA is the process whereby a laboratory's analytical performance is assessed with respect to its peers using analytical material obtained from an external provider such as a United Kingdom National External Quality Assessment Scheme (UKNEQAS)

GLP taken from the respective standards, some of the common factors may be summarised as follows:

- Management driven
- Defined QA/QMS programme
- Defined QA/QMS personnel, independent of process
- Documented procedures (SOPs) for QA/QMS activities and document control
- Defined QC and EQA procedures
- Quality improvement programme.

#### **11.4.2 An Example of a Quality Management System for the Clinical Laboratory**

An example of a QMS that has been implemented in a clinical laboratory to satisfy the QA requirements of the standards discussed is briefly illustrated here. For clinical research laboratories involved in non-clinical studies, strict observance with the GLP principles of QA may be more appropriate.

The QMS is based on one that has successfully been implemented within a clinical laboratory with over 10 years' experience of accreditation and compliance with the types of standards under discussion.

Within each of the standards there are many other factors involved in gaining compliance but the QMS presented provides a firm foundation for success.

The QMS was designed with the latest CPA standards in mind and as such might be that encountered when auditing a CPA accredited laboratory. As such, it should be applicable with GCP requirements. It may also be suitable for use with CAP, ISO 15189 and GLP standards with specific relevant modifications pertinent to those standards.

#### **11.4.3 Requirements for the Quality Management System**

In addition to the standard's QA requirements, there are two fundamental requirements for the success of a QMS:

- It must be fully supported by management and the QMS personnel be granted suitable seniority to enable them to function
- It must be adequately resourced in terms of budget, time and personnel.

A quality manual is required for CPA (and UKAS) that provides the laboratory's definition of the quality policy and quality management, presents the organisational structure and offers an index to the laboratory's documentation.

#### **11.4.4 Implementation**

"Plan, do, check, act" (British Standards Institute).

The QMS was implemented by the laboratory management and appointed quality personnel following a simple plan:

- Decide upon and obtain the appropriate standards
- Management to appoint a quality or QA manager
- Identify QMS personnel responsible for implementing quality improvements
- Prepare management structure including quality management personnel
- Perform baseline horizontal audits (see Section 5) for all departments and disciplines
- Establish laboratory quality policy
- Meet with all management and staff to discuss and describe quality requirements and the implementation process
- QMS personnel to receive training in QA procedures if not experienced

- Prepare audit reports and discuss findings with staff and management indicating clearly the extent of work required to implement quality improvements
- Implement QMS procedures with support of quality management personnel
- Continuous monitoring by audit
- Continuous quality improvement by response to audits, quality meetings and reviewing quality objectives.

#### 11.4.5 Quality Management Group

The main impetus of the system was the provision of a group, led by the quality or QA manager, responsible for the planning, organisation, implementation and direction of the QMS within the laboratory in accordance with the appropriate quality standards. Any quality management group (QMG) must be sufficiently resourced and given the necessary seniority and independence of the laboratory process by the laboratory management in order to carry out its duties efficiently. The QMG was formed from representatives of senior management, consultant pathologists, the laboratory departments and a quality manager.

A line of reporting structure for the QMG is shown in Figure 3. Supported by senior management and consultant pathologists, the laboratory operational group was as follows:

<i>Title</i>	<i>Duties</i>
Quality manager	To plan, organise, effect, administer and monitor the quality management system
Quality coordinators	The quality coordinators were senior members of laboratory staff whose function was to liaise between the laboratories and the QMG and assist with the quality manager's duties
EQA coordinator	To establish, maintain and report from a laboratory database of EQA reports for the QMG

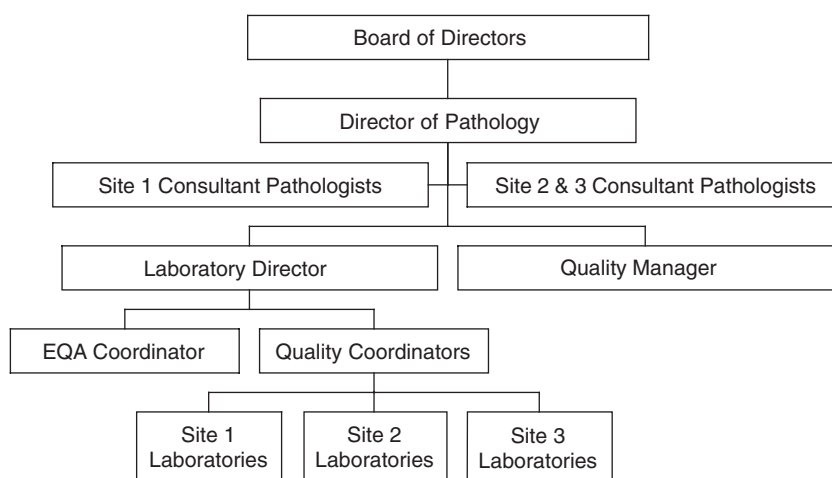
#### 11.4.6 A Quality Policy

A quality policy was produced and was defined as the overall quality intentions and direction of a laboratory with respect to its users, quality and service standards aspired to, and provides a framework to set quality objectives and implement improvements.

#### 11.4.7 The Quality Management Group's Operations

The QMG's operations included, but were not limited to, the following:

- The preparation and maintenance of quality manuals and quality management documentation (SOPs, *etc.*) for all sites
- The preparation and maintenance of SOP indexes for all sites
- The preparation and maintenance of a document and clinical material management systems
- Meet on a regular basis to review all quality matters including internal quality control (IQC), EQA-associated analytical problems, quality standards and training, internal/external audits and their responses and overall quality system management and documentation
- Provision of regular scheduled audits and inspections of the laboratory functions and all areas of the quality system to ensure both a high quality of the data generated and compliance to the required standards
- The provision of expert advice and interpretation on quality matters and relevant standards within the organisation



**Figure 3** A quality reporting structure of a quality management group

- The provision, where necessary, of appropriate quality training to all members of the QMG and staff at all sites within the organisation.

#### 11.4.8 Documentation

The QMS documentation and SOPs included the following titles. The SOPs were cross-referenced to risk assessments and included examples of the necessary forms for carrying out the functions:

- Quality Manual
  - Contents include the following: general information, quality policy, organisation, responsibilities, authorities, quality management system, personnel, premises and environment, equipment and reagents, information systems, pre-examination (analysis) process, examination process, post-examination process, evaluation and quality assurance
- QMG overview and operations
- Procedures for the production and amendment of laboratory quality manuals and QMG SOPs
- Procedures for QMG meetings and EQA review
- QMG personnel and training
- Internal audit procedures (including horizontal audits, vertical audits and examination audits or method witnessing)
- Accreditation QMS audits
- Management review
- Error reporting and complaints procedures
- Archiving
- Maintenance of laboratory SOP indexes and quality records.

### 11.5 AUDITING THE CLINICAL LABORATORY

#### 11.5.1 Introduction

This section is intended to provide practical guidance in auditing clinical laboratories. Laboratory audits may take place in order to evaluate a laboratory prior to its involvement in a study or they

may be performed during a study to ensure continued compliance. All the standards discussed require audits to be performed by the facility's QA component, the sponsor or their agent and ultimately by the accrediting body or compliance authority.

A summary of the above-mentioned definitions of auditing provided by the standards discussed suggests that the audit process should be systematic, independent and documented and comply with the required standards. Therefore, auditing of a laboratory, whether performed by internal or external inspectors, should encompass these elements to assure the sponsor, employer or their agents, that the facility is performing its processes to available protocols and SOPs and is in compliance with the necessary principles.

This section is only concerned with the audit of clinical laboratories and not study plans, protocols or final reports as required by a member of the GLP compliance programme undertaking regulated GLP studies.

Laboratory inspections are also conducted to confirm observance of agreed quality of service standards such as turn-around times, reporting of results, dispatch of specimen collection materials and interpretation of results.

### 11.5.2 Types of Audits

Audits should be performed following an audit plan or schedule. Within a laboratory it is common to structure an annual audit schedule comprising of inspections that cover all disciplines and study requirements within the organisation in a year. If the laboratory is accredited with a number of quality standards, the audits are constructed to accommodate and monitor their specific requirements. Audits may also be performed following an incident or customer complaint or to cover a facility, study or process.

Clinical laboratories tend to use three types of audits as featured by CPA and UKAS. These are as follows:

- Horizontal (or system) audits
- Vertical audits
- Examination audits (or method witnessing).

*11.5.2.1 Horizontal Audits.* Horizontal audits concentrate on a single function or system of the laboratory operation and provide a detailed inspection of all elements of that function with reference to the relevant quality standards. They provide thorough checks of a particular aspect of the documentation and implementation of the QMS or analytical processes and systems.

Each discipline or department (*e.g.* couriers, phlebotomy, specimen reception, individual laboratories, computers, archive, personnel and QA) is individually inspected encompassing the following functions (for reference the corresponding CPA standard is shown in square brackets):

- Facilities [C1]
- Personnel [B3]
- Equipment, materials and reagents [D1/3]
- SOPs [A8/F2]
- Raw data and archives [A9]
- Computer systems [D2]
- Health and safety/security [C5/1]
- General observations including reporting of results
- QA [H].



All records within the elements for each discipline or department relevant to the study are examined and are therefore excellent indicators of a laboratory's exact state of compliance at that time. These are very thorough inspections and so it may be found convenient to audit groups of elements separately. Horizontal audits should be scheduled to cover all elements of all disciplines or departments at least once in 12 months.

**11.5.2.2 Vertical Audits.** Vertical audits follow the specimen of a study retrospectively throughout the laboratory process from specimen collection to reporting and archive of data. They can be performed on all or part of the process and may be started at any point in the process. Vertical audits provide detailed checks that all elements associated with a chosen specimen are implemented and may include, but are not limited to, inspecting the following functions:

- All or some of the areas of the laboratory process (*e.g.* couriers, phlebotomy, sample reception, laboratory areas and functions, analytical procedures, reporting results, QA and archiving)
- All elements (*e.g.* facilities, personnel, equipment and reagents, SOPs, raw data and archives, computer system, health and safety/security, general observations and QA) for all sections or departments through which the specimen passes
- The parity of results, as represented by the final report, with the raw data.

Only the areas of the elements that are relevant to the specimen under investigation are considered. These audits are not as detailed as horizontal audits but provide an excellent overall illustration of the state of compliance of a laboratory or process. They are particularly useful for sponsors or their agents for monitoring a facility during a study. Vertical audits should be performed at least once for each study and should include all disciplines at least annually.

**11.5.2.3 Examination Audits.** Examination audits are where a method or procedure being performed by a trained operator is witnessed by someone familiar with the process with reference to documented procedures. Their purpose is to ensure that either the process or procedure being performed is being carried out in accordance with the SOP or the SOP is a true and accurate account of the procedure being monitored. They also make sure that the trained operator carrying out the examination has a thorough understanding of all aspects of the procedure.

QA personnel may perform the audits but, as their understanding of the procedures may be limited, they are probably best performed by other trained operators under the auspices of QA personnel. Examination audits should be scheduled to include each method or procedure performed by the laboratory or department at least once annually.

### **11.5.3 An Audit Checklist for Good Clinical Practice/Good Laboratory Practice in the Clinical Laboratory**

The following shows audit elements from which an audit checklist may be designed for use in the clinical laboratory undertaking clinical trials. As with GCLP they are based on the laboratory requirements of the current GLP regulations but include elements commonly encountered in hospital type laboratories. The elements include references to the main CPA standards, shown in square brackets, for those unfamiliar with these. The elements may be used individually, in groups or systematically for horizontal or vertical audits.

During audits ensure that all written records have been made accurately and legibly and are signed/initialled and dated. Changes to raw data, including computer records, must not obscure previous entries; ensure that the changes have been signed/initialled and dated and reasons for the change are shown where applicable. Ensure procedures concur with relevant SOPs.

#### 11.5.3.1 Facilities.

- Check floor plans to ensure that the location and construction of the laboratory meet the requirements of the procedure [C1]
- Ensure space is sufficient to separate procedures [C1]
- Check for sufficient storage room for supplies and equipment, separate from procedures and protected against deterioration [C4]
- Ensure environment is conducive to efficient and comfortable work. Check the general standard of housekeeping [C1/5]
- Are the facilities secure against unauthorised access [C1.3]?

#### 11.5.3.2 Personnel/Administration.

- Obtain organisation charts [A1.4]
- Examine CVs, job descriptions, induction, training records and evidence of continued education (e.g. attendance at internal/external courses) of relevant staff with training policy/SOP. Ensure they are adequate, current and signed and dated by the employee and supervisor [B3/4/5/6]
- Is there a signature log [B6]?
- Are human resources adequate [B2.1]?

#### 11.5.3.3 Equipment.

- Identify main instrumentation. Check adequacy, validation documentation, comparison studies, validation of computer links and cleanliness [F1/D1/2]
- Check that logs for routine and unscheduled maintenance, cleaning, calibration, standardisation and reagents are correctly completed, signed, dated, actioned and countersigned where necessary. Check for evidence of service contracts [D1.2/1.3/D3]
- Check that temperature logs for refrigerators, freezers, heating blocks and water baths are correctly completed, signed, dated, actioned and countersigned where necessary [D1.2]
- Check pipettes and thermometers to ensure all calibration, accuracy checks and maintenance records are correctly completed, signed, dated, actioned and countersigned where necessary [D1.2]
- Ensure standards, calibration and accuracy check systems certificates are current and to national or international standards [D1.2]
- Ensure all relevant equipment displays a label giving the date of next calibration, maintenance or service; equipment not in use should be labelled as such [D1.2/1.3]
- For reagents, ensure that date of receipt and quantities received are recorded [D3.2]
- Check reagents for correct labelling (e.g. identity, concentration, storage conditions, lot number, expiry date, preparation date, stability) [D3.3]
- Ensure audit trails exist for analytical procedures identifying individual samples with equipment and reagents used and operators [A9.4]
- Check IQC material used, frequency of analysis, derivation of ranges and acceptance/rejection procedure [F3].

#### 11.5.3.4 Standard Operating Procedures.

- Ensure that, in addition to analytical or process SOPs, there are SOPs for SOPs, staff induction and training, archiving and retention of clinical material, IQC and EQA and authorising and reporting of analytical results [A8/B3/A9/F3/F2/G]
- Is there an index of SOPs indicating issue date and review status [A8.1]?

- Ensure SOPs are current, authorised/approved by management and reviewed within required period [A8.1]
- Check that relevant SOPs are in their correct positions and current by discussion and/or method witnessing [A8.2]
- Check for unauthorised or superseded copies, ensure amendments are authorised and dated [A8.1]
- Check for unauthorised “memory aids” [A8.1].

#### *11.5.3.5 Raw Data/Archive.*

- Ensure records are being kept and signed/initialled and dated. Check archive system for raw data and clinical material. Check SOP for details of storage, record keeping and retrieval [A9/D2]
- Check audit trail for computer captured raw data, release and amendment of results [D2]
- Ensure archive location, design and conditions protect contents from damage [A9.1]
- Ensure archive index and inventory systems facilitate orderly storage, retrieval and replacement [A9.1]
- Ensure access is limited to authorised personnel and records of access are kept [A9.1].

#### *11.5.3.6 Computer System.*

- Check for full description of system, documentation/SOPs including operations, maintenance and disaster recovery [D2.2]
- Ensure procedures exist (where necessary) for development, validation, validation of instruments to main system, change control and subsequent/periodic testing, validation of results transmission software [D2.2]
- Check physical security of system and access to programs and ability to change data, ensure audit trails and archives [D2.2]
- Check data backup and retrieval system [D2.2].

#### *11.5.3.7 Result Audit.*

- Ensure results agree with raw data (check dilutions and correction factors)
- Check IQC procedures with practice and recent performance against designated limits [F3.1]
- Check EQA performance and procedures to ensure it is in accordance with scheme organisers’ recommendations [H5].

#### *11.5.3.8 Health and Safety/Security.*

- Is health and safety policy available, accurate and up-to-date [C5]?
- Ensure policy has been communicated to all staff [C5.2]
- Check staff health surveillance policy [B6.2].

#### *11.5.3.9 General Observations.*

- Check to ensure contracts exist between parties and external service providers [A2]
- Check time of arrival of specimens, courier/postal service, number of specimens and time taken to report against service-level agreements [E5.1]
- Monitor specimen-handling procedures. Are specimens uniquely identified and is the identification not reusable [E5.1]?
- Check contingency plans for power failure, computer breakdown or laboratory disaster

- Inspect sample kit preparation. Check QC procedures, audit trail of expiry dates of consumables and signatures of packers/operators [E3]
- Ensure liability insurance exists for the facility [A1].

#### 11.5.3.10 *Quality Assurance.*

- Check laboratory accreditation
- Is there a documented QA programme [A4/H1.1]?
- Is QA independent of the analytical process and reports directly to senior management [A7]?
- Does QA conduct inspections of the facility and record and report audit findings [H1]?
- Check action taken by QA when deviations are found [H3/4/6]
- Does QA have any involvement in the referred or the contracted analyses [E6]?

### 11.5.4 **Reference Ranges, Validation of Examination Procedures, Internal Quality Control and External Quality Assessment**

**11.5.4.1 *Reference Ranges (Normal Ranges).*** Reference ranges are provided by the laboratory for all tests. Reference ranges represent the likely frequency of a pathology result for a healthy individual. They are usually provided by the manufacturer of the test used and are obtained from a healthy population of similar sex and ethnic and socio-economic origin to that of the user group. Some laboratories may derive their own reference ranges if they have access to large amount of data obtained from health screening centres or there is little published data for a specialist test. When considering reference ranges it is important to understand that they may be also affected drastically by age, drinking and smoking habits. These are defined before the start of analysis on the study.

**11.5.4.2 *Validation of Examination Procedures.*** Examination procedures (tests or analyses) are validated for their intended use before a procedure is introduced or changed. Validation should also be performed before the introduction of new equipment (including computer equipment, see Chapter 37) or following significant changes thereof. CPA defines validation as “Confirmation and provision of objective evidence that the requirements for a specific intended use or application have been fulfilled”.

The methods used for validation may consist of reproducing the manufacturer’s performance claims for within and between analysis variation and determining accuracy through the use of EQA samples. For in-house methods, recovery and stability experiments may also be performed. When methods, procedures or equipment are changed, validation may take the form of comparison studies between the two systems. Method comparisons may be performed using patients’ samples to evaluate the bias (difference between the means of a series of samples analysed on both systems). The National Committee for Clinical Laboratory Science (NCCLS, USA) produces a definitive guideline for method comparisons. Acceptance of validation results may be influenced by many factors including analytical superiority, ease of use, cost, speed of analysis, use of hazardous materials and type of specimen required. The results may lead to a change in reference ranges that could cause problems of continuity of data if carried out during a study. It may be difficult for an auditor to interpret a validation or comparison experiment in order to make a judgment with regard to its scientific integrity in which case expert advice should be sought. The auditor should ensure that the experiments have been fully documented and the results and conclusions recorded are signed and dated by the operators and management. All records should be kept for the designated retention period according to the relevant accreditation or regulatory requirement.

**11.5.4.3 Internal Quality Control.** IQC may be used for qualitative (positive or negative results) or quantitative (numeric results). The latter may involve the use of a single or up to three levels of material within an analysis. An analysis may be accepted as having performed correctly if the values of the IQC samples fall between pre-derived ranges. A laboratory may use the manufacturer's ranges of IQC values with which to verify the test or they may establish their own. Acceptance ranges (limits) are usually established as  $\pm 2-3$  standard deviations from a mean value. More sophisticated systems are occasionally used which rely on the analysis of IQC trends across time and the levels of material (*e.g.* Westgard).

Auditors should ensure procedures for the use, derivation of ranges and acceptance of analyses are available and are being followed.

**11.5.4.4 External Quality Assessment.** EQA (see Table 2 for definition) in the UK is mainly organised under the auspices of United Kingdom External Quality Assessment Service (UKNEQAS). UKNEQAS schemes are accredited by CPA and are organised and operated by clinical laboratories mainly within the NHS. These distribute samples for analysis by participating laboratories and also analyse a laboratory's performance with respect to a consensus.

Scheme organisers publish details of accepted performance criteria that auditors should use to establish individual analyses and overall scheme proficiency. As with IQC, auditors should ensure procedures for the use, interpretation and subsequent action are available and being followed. Satisfactory EQA performance can only occur following a well-designed and appropriately executed IQC procedure.

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## **Part 2: Good Laboratory Practice**



## CHAPTER 12

# Introduction: Good Laboratory Practice

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## 12.1 INTRODUCTION

The admission of chemicals and chemical substances on national markets is strictly regulated in most developed countries. This means that companies seeking permission to place their products on the market have to go through tedious processes to reach that goal. Regulatory authorities will normally require substantial data sets on physical and chemical properties and on the safety for humans, animals and environment of chemicals, such as industrial chemicals and pesticides. For other chemical products such as human medicines and often also veterinary drugs, the information to be submitted must also include data on efficacy, pharmacokinetics *etc.* To obtain these data clinical trials in humans have to be carried out. These trials must be performed in accordance with the regulations for good clinical practices (GCPs). The non-clinical (or pre-clinical) studies, as they are called relating to pharmaceuticals, or safety studies, as they are known for other chemicals, need to be performed in accordance with the regulations for good laboratory practice (GLP).

The Organisation for Economic Cooperation and Development (OECD) has defined GLP as follows: Good laboratory practice is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.<sup>1</sup> Furthermore, it is stated that “unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulation for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals”.

GLP is thus a quality system in the same line as other quality systems, but restricted to the research that is done for regulatory purposes. The application is usually required by law and/or regulations, whereas the enforcement is monitored by or on behalf of governmental authorities and agencies.

Governmental bodies are normally responsible for the licensing or regulation of chemicals and chemical products. They have to evaluate all the required information in order to reach a deliberate decision, and therefore must be able to trust the data, as they have been submitted, fully. Study reports must faithfully and integrally reflect the raw data and study records.

## 12.2 HISTORY

Not the United States, but rather small countries were the first to address this issue formally. New Zealand in 1973 promulgated the Testing Laboratory Registration Act, which defined “the testing

laboratory” to include staff records, procedures, equipment and facilities. The act also established a testing laboratory registration council, with functions and powers “to promote the development and maintenance of good laboratory practice in testing”. And Denmark approved, in March of the same year, legislation addressing laboratory practices in “the law about the states technical trial board”, which defined the duties of the board as advancing, promoting and co-ordinating technical experiments for the purposes of bringing about safety and quality control.

But the formal concept of GLP as it is now, did firstly evolve in the United States.

In July 1975, during a hearing of the subcommittee of health of the senate judiciary committee, chaired by Senator Edward Kennedy, certain Food and Drug Administration (FDA) employees made allegations of improprieties on the part of Searle Laboratories in conducting and reporting animal safety tests. In order to resolve these allegations the FDA undertook a thorough investigation of pre-clinical research at Searle, with which Searle agreed to co-operate fully. The investigation began in October 1975 and lasted for some months, with as many as 20 FDA investigators on site at any one time. A similar investigation was taking place concurrently at Hazleton Laboratories (USA), a contract laboratory used by Searle to conduct studies. Arising from the questions and queries raised during this investigation, a number of scientists from Searle developed a document entitled “Good Laboratory Practice”, which was designed to deal with the documentation of laboratory activities and the provision of standards against which laboratory activity could be evaluated. This was submitted to the FDA and Pharmaceutical Manufacturers Association (PMA) in January 1976.

In subsequent hearings by Senator Kennedy in April 1976, additional funding was requested for further investigation. This was granted by Congress and 606 new positions were created especially for monitoring biological research. This programme became known within the agency as the Bioresearch Monitoring Programme. In August 1976 the FDA released a draft set of GLPs based on the Searle document, and on 19 November 1976 the proposed GLP regulations were published in the Federal Register (1976). After this publication the FDA instituted a pilot programme of inspections, beginning in December of that year, designed to develop a baseline to measure the conformance of laboratories to the proposed GLPs and to obtain additional knowledge about the current status of laboratory practice in the testing industry. Forty-two laboratories were inspected originally. Inspections were later extended to cover some 78 laboratories, including some outside the United States. The FDA found that some studies submitted had not been conducted in accordance with acceptable practices, and as such were not of a quality and integrity to assure product safety. Primary non-compliance with the proposed regulations was caused by facilities failing to have a quality assurance (QA) unit, failing to test each batch of test articles, carrier mixture, and a lack of standard operating procedures (SOPs). It was not surprising to find the lack of a QA unit as a main problem, as QA was a relatively new concept, and in many operations the writing of formalised SOPs was a major task not yet completed. Based on this experience and discussions with industry and trade organisations, the final GLP regulations were published in the Federal Register on 22 December 1978. They became a legal entity in the United States on 20 June 1979 (21 CFR 58). Changes to the US GLPs were proposed on 24 October 1984, primarily in the provisions on QA, protocol preparation, test and control article characterisation, and in the retention of specimens and samples. Publication of the revised GLP regulations took place on Friday, 4 September 1987, in the Federal Register, and were entitled “Good Laboratory Practice Regulations, The Final Rule”.

In the first years of compliance monitoring after the introduction of GLP in 1979, the justification of establishing GLP requirements became obvious from the inspection results. Although for the most part the health and safety testing in industry worked (and is still working!) to a very high standard, there were a few cases where this was not so. The two best-known examples of very bad practices and even fraud were found in two contract research companies in the United States, Biometric Testing Incorporated and Industrial Bio-Test Laboratories. In the case of Biometric

Testing Incorporated, after extensive investigations by FDA, two former vice-presidents pleaded guilty of conspiring to falsify reports of animal tests on certain drug products, in order to show them harmless, when in fact the tests had not been carried out. The company eventually became bankrupt. Certainly the most celebrated case uncovered by the FDA during its early investigations was the second mentioned, that of Industrial Bio-Test (IBT) Laboratories. This laboratory was at the time the largest contract-testing laboratory in the world and had conducted, over a long period, many hundreds of pre-clinical safety studies, mostly for the pesticide industry. Some 20,000 studies to support the safety and efficacy data were generated for hundreds of drugs and pesticides. The irregularities in data were numerous, and included falsification of laboratory work: replacement of animals that died under test with fresh animals without documenting their substitution, fabricating test results and excluding test results if they were unfavourable to top company officials. Three company officials were found guilty of defrauding the government by falsifying drug and food additive research data. Their appeal to the Supreme Court was denied in 1986, and all were given lengthy jail sentences. Extensive investigations by the Environmental Protection Agency (EPA) and the Canadian Health Authorities concluded that most of the long-term studies conducted by IBT were invalid. The chemical industry was required to repeat these if it wished to keep its products on the market. For many companies this resulted in the expenditure of many millions of dollars and pounds. Needless to say, IBT as a contract-testing laboratory no longer exists. A summary of the observations seen during these inspection periods plus conclusions as to the unsatisfactory nature of experimental testing follows.

### 12.2.1 Observations

- (i) The original post-mortem records for studies carried out at the contract organisation were unavailable or apparently transcribed to new records several years after the post-mortems had been carried out.
- (ii) The reports from the pathology group submitted to the agency were found to be inconsistent with the original records obtained at post-mortem.
- (iii) The slides when subjected to microscopic examination were investigated by more than one pathologist. Each of the pathologists when examining the tissue slides came to different conclusions: the conclusions that were favourable to the drug, however, were the only ones submitted to the agency.
- (iv) Observations of data analysed within the laboratory and forming the basis of raw data records were neither dated nor signed.
- (v) When confronted with discrepancies between raw data and final reports submitted to the agency, employers were unable to account for the problems and discrepancies.
- (vi) A variety of factors were recorded as normal in observed animals, including diet consumption, animal appearance and water consumption, when in fact the animals were dead.
- (vii) Animals who received a drug under test, received this drug in a manner that made it impossible to determine how much of the required dosage was actually given to the animal, if any at all.
- (viii) At one of the establishments investigated by the agency, teratology and reproduction studies were conducted and the laboratory personnel were overseen by a senior member of staff. This senior scientist did not have proper qualifications or background to be supervising, let alone conducting these critical studies.
- (ix) Animal weights were not accurately recorded.
- (x) Control animals and treated animals were not properly identified.
- (xi) Necropsies were performed by people who had received no proper training nor were they overseen by a senior scientist to review their work.

- (xii) One contract-laboratory study had serious questions raised about the conduct of the study. Management, however, having serious questions about the conduct of the study neither posed these questions nor exercised any control of the operating investigator.
- (xiii) An animal facility was treated with pesticides to remove vermin while the animals were still present in this complex.
- (xiv) Animals at sacrifice were fixed in total and not subjected to necropsy for several months following sacrifice.
- (xv) Again in a study carried out by a contract laboratory, FDA was informed that animal tissue had been examined histopathologically. When carrying out a review of this laboratory's original records, it was found that these tissue samples were never collected.
- (xvi) Again at post-mortem, gross observation on the pathology sheets when compared with individual pathology summaries produced by the pathologist were submitted to the agency, several significant discrepancies were found between these two sets of data.
- (xvii) An indication that management did not perform their duties in checking data produced was identified when a firm submitted a study to the agency utilising the wrong data and the wrong animal identification numbers. This was first discovered by the agency, not the management of the testing facility.

The conclusions from these findings can be summarised as follows:

- (i) It was ascertained that following the observations, assurance could not be given for the scientific qualifications and adequate training of personnel involved in the studies.
- (ii) Experiments were poorly conceived, carelessly executed, inaccurately analysed and poorly reported.
- (iii) Technical personnel being unaware of the importance of the protocol adherence did not keep accurate observations and accurate administration of the test substance, nor accurate records with regard to raw data and transcription of records.
- (iv) At the critical review of data stage, management did not assure that this took place or that there was proper supervision of personnel.
- (v) Several firms failed to verify the accuracy and completeness of scientific data in non-clinical laboratory reports in such a systematic manner to preclude error before submission to the agency.
- (vi) There was a total disregard for the need to observe proper laboratory facility operation, care in the animal facility and data-management procedures.
- (vii) Sponsors were at fault for failing to monitor adequately the studies that were carried out in contract research facilities.

Several laboratories subject to the FDA's monitoring activities were contract laboratories, also involved in studies, intended for eventual submission to the EPA in the context of the regulation of pesticides or industrial chemicals. The EPA therefore not only cooperated with the FDA, but also started to monitor the test facilities on its own. Proposals for GLP regulations were published in 1979 in the framework of the Toxic Substances Control Act (TSCA) and in 1980 for the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), whereas the Final Rules were published in 1983.

Of course, this process of the genesis of GLP did not go unnoticed outside the United States; moreover since several non-US laboratories were involved in the FDA monitoring activities. Table 1 gives an overview of the most important developments in GLP legislation.

Globally, the most influential activities were initiated under the umbrella of the OECD.

The OECD, an intergovernmental organisation grouping 30 industrialised countries, has been involved in the harmonisation of policies and instruments for chemicals control since the late 1970s.

**Table 1** Important events in the history of GLP

1972	New Zealand	Testing Laboratory Registration Act
	Denmark	National Testing Board Act
1976	US-FDA	GLP Proposed Rule
1978	US-FDA	GLP Final Rule
1979	OECD	Expert Group on GLP
	US-EPA	GLP Proposed Rule TSCA
1980	US-EPA	GLP Proposed Rule FIFRA
1981	OECD	Council Decision on Mutual Acceptance of Data (MAD)
1982	OECD	GLP Principles published
	Japan-MHW	GLP Notification
1983	US-EPA	GLP Final Rules (TSCA and FIFRA)
1984	Japan-MITI	GLP Notification
	Japan-MAFF	GLP Notification
1985	EC	Proposal GLP Directive
	US-FDA	Revised GLP Final Rule
1987	EC	Directives 87/18, 87/19, 87/20, 87/153
1988	EC	Directive 88/320
1989	EC	Directive 89/569
	US-EPA	Revised Final Rules TSCA and FIFRA
	OECD	Council Decision C(89)87(Final)
1990	EC	Directive 90/18
1991	EC	Directive 91/414
1992	OECD	Consensus Documents on QA, Suppliers, Field Studies
1993	OECD	Consensus Documents on Short Term Studies, Study Directors
	EC	Directive 93/35
1995	OECD	Consensus Document on Computerised Systems
	OECD	Revised Guide for Compliance Monitoring Procedures for GLP
	OECD	Revised Guidance for the Conduct of Laboratory Inspections and Study Audits
1997	OECD	Council Decision C(97)114(Final)
1998	OECD	Advisory Document on Role and Responsibility of Sponsor
	OECD	Revised GLP Principles
	EC	Directive 98/8
1999	EC	Directives 1999/11 and 1999/12
	OECD	Publication of Revised Consensus Documents
2000	OECD	Advisory Document on Requesting Inspections and Study Audits in Another Country
2002	OECD	Consensus Document on Multi-Site Studies
2004	EC	Directive 2004/9
	EC	Directive 2004/10
	OECD	Consensus Document on <i>in vitro</i> Studies

One of the results of the cooperative efforts of the member countries of the OECD has been, and still is, the development and updating of the OECD Test Guidelines. Also the importance of the quality and reliability of test data was recognised by the OECD, triggered by the FDA's bio-monitoring programme. The OECD Council decided to set up a Special Programme on the Control of Chemicals, with a Management Committee to supervise the work under the Programme and to set up an Expert Group to work on GLP. This Expert Group, with the United States as lead country, had completed the so-called principles of GLP in 1980. On 12 May 1980, on the proposal of the High Level Meeting of the Chemicals Group, endorsed by the Environment Committee, the OECD Council adopted the Decision concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30 (Final)]. The Council decided:

“that data generated in the testing of chemicals in an OECD country in accordance with OECD Test Guidelines and the OECD Principles of Good Laboratory Practice shall be



accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment”.

In support of this decision, the Council recommended that member countries should apply the OECD Test Guidelines and the Principles of GLP when testing chemicals. What has eventually made the OECD GLP system so important is that the Management Committee was further instructed to develop internationally-harmonised approaches to assure compliance with the OECD Principles of GLP. In keeping this instruction, the Expert Group prepared a review on “The implementation of the OECD Principles of Good Laboratory Practice”, which presents the elements considered necessary for the establishment of effective national GLP compliance monitoring programmes and their mutual recognition. In a revised form this review can be found in the OECD series on GLP.<sup>2</sup> Further, the group believed that national compliance schemes needed two tools: test facility inspections and study audits. So they developed guidelines for the conduct of those, which now can be found, again revised, in the OECD series.<sup>3</sup> These documents have served and still do so, in harmonising monitoring practices worldwide in OECD and non-OECD countries and are of tremendous value in the mutual recognition of monitoring programmes as well as the mutual acceptance of data (MAD).

### 12.3 MUTUAL ACCEPTANCE OF DATA

As already touched upon above, the main motive for OECD to develop the GLP principles (and the OECD Test Guidelines) was to facilitate that data generated in the testing of chemicals in one country would be accepted in other OECD member countries. The first Council decision addressing this issue was Decision C(81)30(Final), merely compelling member countries to accept these data, whenever the OECD test guidelines were applied and the GLP principles were followed. By Council Decision-Recommendation C(89)87(Final) additional conditions were set forth. The OECD member countries were obliged to establish national procedures for monitoring compliance with the GLP principles and to designate at least one authority to execute these monitoring functions. Furthermore the member countries were required to set up a system for the exchange of information on their national procedures, and most importantly, on the exchange of information concerning GLP compliance of test facilities (including information focusing on particular studies). As a result of this all OECD member countries, with significant testing laboratories, have set up one or more monitoring authorities. A third Council Decision, C(97)114(Final) was adopted to meet the commitments made by the Ministers of the Council at ministerial level on 23rd and 24th May 1995 to support the integration of developing countries and economies in transition into the world economy system, so that both member countries and non-member countries would benefit from enlarged participation in the OECD Council Acts related to mutual acceptance of data in the assessment of chemicals. A procedure was developed to let interested non-member countries join this part of the OECD Chemicals Programme. Basically it means that these countries must implement the Council Acts; that is to set up a GLP monitoring programme equivalent to those of the OECD member countries. After 3 years the system will normally be evaluated by representatives of the Member States and, pending a favourable outcome of this evaluation, the country will become a full member of the programme on MAD. So far, three countries have been accepted as full members: South Africa, Slovenia and Israel. One other country, India, is still in the process of setting up a GLP monitoring system. Table 2 gives an overview of all monitoring authorities of the countries in the OECD Chemicals Programme involving mutual acceptance of data.

As can be seen, the organisation of GLP monitoring is quite straightforward in most countries, having one or two authorities. Most of them are governmental bodies, although in quite a number of countries monitoring has been contracted out to accreditation bodies. In some countries the

**Table 2** Overview of monitoring authorities in OECD countries and non-OECD countries adhering to MAD Council Decision

Country	Monitoring authority	Scope
Australia	National Assoc. of Testing Authorities (NATA)	All
Austria	Federal Ministry for Agriculture and Forestry, Environment and Water Management Ministry of Health	Ind. Chem./ Agrochem. Pharm.
Belgium	Scientific Institute for Public Health Louis Pasteur	All
Canada	Environment Canada Standards Council Canada (SCC)	Ind. Chem. Agrochem.
Czech Republic	Centre for Assessment of Laboratories (ASLAB)	Ind.Chem./ Agrochem.
Denmark	State Institute for Drug Control (SUKL)	Pharm./Vet. Drugs
	Danish Medicines Agency	Pharm.
	The Danish Accreditation and Metrology Fund, (DANAK)	Ind.Chem./ Agrochem.
Finland	The National Product Control Agency for Welfare and Health (STTV)	Ind.Chem./ Agrochem.
France	National Agency for Medicines	Pharm.
	<i>Agence Française de Sécurité Sanitaire des Produits de Santé</i> (AFSSAPS)	Pharm.
	<i>Agence Française de Sécurité Sanitaire des Aliments</i> (AFSSA)	Vet. Drugs
Germany	<i>Comité Français d'Accréditation</i> (COFRAC)	Ind. Chem.
	Federal Institute for Risk Assessment (BfR)	All
	<i>Bundesländer</i>	All
Greece	General Chemical State Laboratory (GCSL)	Agrochemicals
Hungary	National Institute of Pharmacy (OGYI)	All
India (prep.)	Department of Science and Technology	All
Ireland	Irish National Accreditation Board (NAB)	All
Israel	Israel Laboratory Accreditation Authority (ISRAC)	All
Italy	<i>Istituto Superiore di Sanità</i> ; (ISS)	All
Japan	Ministry of Agriculture, Forestry and Fisheries MAFF)	Agrochem./Vet. Drugs./Feed Add.
	Ministry of Economy, Trade and Industry (METI)	Ind. Chem.
	Ministry of Health, Labour and Welfare (MHLW)	Ind. Chem./Pharm./ Workpl.Chem./ Med. Devices
Korea	Ministry of Environment (ME)	Ind. Chem
	National Institute for Environmental Research (NIER)	Ind. Chem
	National Institute for Toxicological Research (NITR)	Pharm.
The Netherlands	Rural Development Administration (RDA)	Agrochem.
	Food and Consumer Products Safety Authority (VWA)	All
	International Accreditation New Zealand (IANZL)	All
New Zealand	Norwegian Accreditation ( <i>Norsk Akkreditering</i> )	All
Norway	Bureau for Chemical Substances and Preparations	Al
Poland	Ministry for Industry and Energy; <i>Instituto Português da Qualidade</i> (IPQ)	Ind. Chem./ Agrochem.
Portugal	National Institute for Pharmacy and Medicines (INFARMED)	Pharm.
Slovak Republic	State Institute for Drug Control, Slovak National Accreditation Service (SNAS)	All
Slovenia	National Chemicals Bureau (URSK)	All
South Africa	South African National Accreditation System (SANAS)	All
Spain	<i>Ministerio de Sanidad y Consumo; Division de Inspeccion y Control;</i>	Pharm.
	National Unit for Accreditation (ENAC)	Agrochem.

(Continued)

**Table 2** (Continued)

Country	Monitoring authority	Scope
Sweden	Medical Product Agency, <i>Läkemedelsverket</i> Swedish Board for Accreditation and Conformity Assessment (SWEDAC)	Pharm. Ind. Chem./Agrochem
Switzerland	Swiss Agency for the Environment, Forest and Landscape (BUWAL); Swiss Federal Office of Public Health (BAG); Swiss Agency for therapeutic products (Swissmedic)	All
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	All
United States	Food and Drug Administration (FDA)  Environmental Protection Agency (EPA)	Pharm./Vet. Drugs/ Med. Dev. Ind. Chem./ Agrochem.

**Table 3** Overview of GLP Programmes in Japan (2004)

GLP programme	Ministry	Inspectional body
Pesticides	MAFF	Agricultural Chemicals Inspection Station
Veterinary drugs	MAFF	National Veterinary Assay Laboratory
Feed additives	MAFF	Fertilizer and Feed Inspection Services
Workplace chemicals	MHLW	National Institute of Industrial Health
Pharmaceuticals and medical devices	MHLW	Pharmaceuticals and Medical Devices Agency
Industrial chemicals		
Toxicity	MHLW	National Institute of Health Sciences
Bioacc./Biodegr.	METI	National Institute of Technology and Evaluation
Ecotoxicity	ME	National Institute of Environmental Research

situation is more complex. In Germany the GLP inspections are carried out by authorities in each of the 16 States (Länder), where the Federal Bureau for Risk Assessment, based in Berlin, has a co-ordinating role and carries out inspections abroad. In Japan the situation is more complicated since there are six GLP monitoring programmes, for which four Ministries are responsible, whereas quite a number of institutes are involved in the actual monitoring of GLP compliance (Table 3).

It has been recognised by Japanese officials and industry that this situation leads to too many inspections and multiple inspections as well as inconsistencies in the interpretation of GLP requirements by various inspectors. So now there is a growing willingness to simplify and to harmonise the monitoring system.

Other countries, such as Switzerland and Korea, have set up single monitoring programmes, which are executed jointly by the responsible Ministries and/or agencies.

The essence of the OECD MAD system, in practical terms, is that safety data produced in one country are accepted in another country, under the following conditions:

- the data must have been produced in accordance with the OECD Principles of GLP, which is claimed for in writing by the study director;
- there must be a functioning monitoring authority in the country, where the data are produced;
- the test facility must be included in the monitoring programme of that country.

Obviously, receiving (regulatory) authorities have the right to request specific study audits, especially where it concerns pivotal studies, but generally studies are accepted if the above conditions are satisfied.

## 12.4 THE SCOPE OF GLP

As mentioned above, GLP should be applied to environmental and non-clinical safety testing of all chemicals and preparations for regulatory purposes. The chemicals involved can therefore be human medicines, veterinary drugs, industrial chemicals, animal feed additives, food additives and pesticides including biocides and cosmetics. At national levels the application of GLP can be extended to the testing of other chemicals or even to non-chemicals. For instance, the US-FDA regulations require that all safety testing of medical devices be done under GLP, which is also true for the Japanese regulations. The types of research subject to GLP include toxicity studies, ecotoxicity studies, environmental fate and bioaccumulation studies, analytical chemistry, clinical (pathological) chemistry, pharmaco- and toxicokinetic studies, the determination of physico-chemical properties, residue studies and studies of effects on mesocosms and ecosystems. However, this range varies between countries, since laws and regulations are not the same in two countries. Precise information can of course be obtained from the relevant regulatory authorities.

## 12.5 LEGISLATION

Of course the requirements to apply GLP, as well as the task of monitoring the application of GLP, is laid down in national laws and regulations. In the United States the GLP requirements for the FDA programme are set out in the Federal Register (21 CFR Part 58), published on 4 September 1987. These requirements are based upon the Federal Food, Drug and Cosmetic Act and the Public Health Service Act. The requirements for the EPA programme are laid down in the Federal Register (40 CFR part 160 for the Federal Insecticide, Fungicide and Rodenticide Act, and 40 CFR part 792 for the Toxic Substances Control Act, both effective on October 16, 1989. EPA has proposed (December 29, 1999) a Rule to combine FIFRA and TSCA (40 CFR 806), but this proposal is still on the shelf at the time of publication of this book.

In the European Union, the requirement to apply GLP was first published in 1987 in Directive 87/18/EC, whereas the obligation to monitor GLP compliance was laid down in Directive 88/320/EC (1988). After several update codified versions of these Directives, replacing and superseding all former directives on these subjects, were published in 2004, as Directives 2004/9/EC and 2004/10/EC (both of February 11, 2004).<sup>4</sup> The EU Member States are obliged to transpose the Directives into their national laws and regulations, and almost all have done so loyally. Details of the legislation can be obtained from the national monitoring authorities.

Also other OECD member countries, and the non-member countries participating in the MAD system, have the requirements to apply GLP to non-clinical safety studies and their GLP monitoring system embedded in their own legislation. A thriving force to do so has been the Mutual Joint Visit programme that has been set up by the OECD GLP Working Group. This programme, although a pilot project, was initiated to build up confidence between monitoring authorities internationally and has been extremely useful to enhance legislative and administrative instruments related to GLP.

It must be added here, that a number of developing countries are now quite eager to initiate or to complete GLP systems, not only to keep up with international standards for health protection, but also to assist their national industry and test facilities to have their data accepted internationally. Examples are India, that has been setting up a system for a couple of years now; Brazil, that already has a GLP system, but is now getting it into line with the OECD MAD system; Singapore; China and Chinese Taipei, which are very interested and having working contacts with the OECD; Romania, that is also in the process of completing its GLP system. The OECD, through the Working Group on GLP is heavily involved in these processes by assisting these countries in various ways.

## 12.6 ROLE AND ACTIVITIES OF THE OECD WORKING GROUP ON GLP

Under the supervision of what is now named the OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, a GLP Panel has been in existence since 1988 and in 2000 this panel was named “Working Group on GLP”. This working group includes persons, nominated by governments, who are responsible for GLP monitoring, predominantly heads of GLP monitoring authorities. The objectives of the Working Group are to facilitate and support the implementation of the OECD Council Acts as mentioned earlier. The group deals with the direct exchange of information on GLP compliances in their respective territories, tries to resolve issues of international recognition, fosters harmonisation and development of specific guidance on technical and administrative matters pertaining to the GLP principles and GLP monitoring and assists non-member countries in establishing GLP monitoring authorities.

Notably the development of consensus documents on the interpretation of the GLP principles in certain areas is a major task, in which also representatives of industry are involved. Normally a so-called consensus workshop will be organised, the outcome of which, a draft consensus document, will then be presented to and endorsed by the Joint Committee, after which the document will be published.

Other than the GLP principles themselves, the guide for monitoring procedures and the guidance for the conduct of inspections and study audits, these consensus documents are not legally binding. But, since these interpretations are the results of thorough discussions between industry representatives, regulators and inspectors, with which all participants of that workshop have agreed upon, and since such a document is endorsed by the national representatives in the Joint Meeting, they are morally binding both the industry to monitoring authorities.

Over the years seven consensus documents have been published, with the following titles:

- (i) Quality Assurance and GLP;
- (ii) Compliance of Laboratory Suppliers with GLP;
- (iii) The Application of the GLP Principles to Field Studies;
- (iv) The Application of the GLP Principles to Short-Term-Studies;
- (v) The Role and Responsibilities of the Study Director in GLP Studies;
- (vi) The Application of the Principles of GLP to Computerised Systems; and
- (vii) The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies.

Furthermore four advisories and guidance documents have been published:

- (i) Guidance for the Preparation of GLP Inspection Reports;
- (ii) The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP;
- (iii) Requesting and Carrying Out Inspections and Study Audits in Another Country; and
- (iv) The Application of the Principles of GLP to *In vitro* Studies.

All these publications are available from the OECD, both in print and in electronic form from the OECD website.<sup>5</sup>

## 12.7 INSPECTIONS AND CERTIFICATION

The GLP inspectorates will normally conduct test facility inspections once in 2 or (like in Germany) 3 years. These inspections will be quite thorough, and may last 10 or more working days, where it concerns large test facilities. The inspectors will go through all documentation and processes, related to the performance of GLP studies, and will audit a number of on-going or completed

studies. At the conclusion of the inspection, the inspectors normally will present their findings. Most inspectorates will not immediately decide on the compliance status of the test facility, but do so after they have acknowledged the remedial actions (to be) taken. Detailed procedures can be found in the OECD Guidance monograph on the conduct of inspections and study audits. Apart from these regular routine inspections, GLP monitoring authorities also will sometimes conduct study audits on request of national or foreign regulatory authorities. In those cases the studies will be audited in much more detail than is the case at routine inspections.

The GLP system is not a laboratory accreditation system. First, test facilities are, in the GLP area, not inspected primarily to determine if they have the competence to carry out certain tests, but rather to determine if they have operated in such a way that the studies performed are reliable and can be reconstructed from the underlying raw data and study records. Second, laboratory inspections and study audits are carried out for the benefit of public health and the environment for regulatory purposes, and not meant to demonstrate publicly the competence of the test facility in certain areas of expertise. Consequently, there is no obligation in the OECD or EC regulations that a certificate should be issued, after a successful inspection. However, a number of monitoring authorities do issue “certificates”, copies of which then can be used to be included in final study reports to show that the test facility is included in a national GLP monitoring programme. A certificate is however never a guarantee that data produced will be automatically accepted by regulatory authorities. They only indicate that the test facility was operating in compliance with the GLP principles at the time of the inspection.

## REFERENCES

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## CHAPTER 13

# Quality Assurance in GLP

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### 13.1 INTRODUCTION

The quality of a study will depend on the appropriateness of its design, its skillful conduct in accordance with the study plan and standard operating procedures, and the accuracy and scientific integrity of the final report. These in turn are influenced by the calibre of the staff, facilities, equipment, services and materials involved in the study. Arguably, the most important of these is the human element, because quality work results from the efforts of people who are qualified, trained and motivated to discharge their responsibilities to do a good job.<sup>1</sup> Quality can only be achieved as an integral part of each activity; it is concerned with reliability and the prevention of errors and cannot be applied as a veneer by inspections and audit procedures aimed solely at correcting errors. Achieving quality is a team effort demanding the commitment and co-operation of all staff. All laboratory personnel therefore carry the overall responsibility for Good Laboratory Practice (GLP) but it is important to understand the different contributions from the various roles. In this regard GLP identifies four kinds of personnel that are integral to proper experimentation.

### 13.2 MANAGEMENT RESPONSIBILITIES

Usually 'management' occupies a position in the organisational hierarchy above both the study director and the quality-assurance director. Senior managers are those individuals who can authorise funding, dictate structure, and possess the authority to decide between different scientific and commercial priorities. They are also responsible for setting the culture of the laboratory and for establishing the policy framework within which GLP operates. It is they who can authorise corrective actions to rectify strategic shortcomings.

More specifically, management decision usually precedes the initiation and conduct of a study, and management must approve the submission of the final report to a regulatory authority or to a client who has paid for the work. Once a study has been approved it is the management who must select a qualified individual to serve as the study director, based on an awareness of the study objectives and requirements, as well as the personal qualities and anticipated work load of the selected individual.

At the same time the management should identify an individual to serve during extended absences of the study director. These individuals usually carry titles such as 'deputy study director' and 'acting study director'. Next, management should have a procedure for dealing with the replacement of a study director who leaves the laboratory or is reassigned while a study is in progress and before the completion of the final report. The procedure requires a positive notation

in the study records which identifies the replacement study director, the date of the replacement, and the reason for the replacement. Often, an amendment to the study plan (see Chapter 15) reflecting this information is issued. Management should also implement and conduct an effective system of Quality Assurance (QA). There should be procedures to staff the QA unit adequately; performance defects are properly detected, reported, and acted upon; and periodic evaluations of the effectiveness of the quality-assurance system are made. Management should take responsive action, based on the findings of the periodic evaluations and in correcting the performance defects, regardless of their source.

Management must assure that all study staff clearly understand the functions that are listed in their job descriptions. This requires a documented personnel training and development plan, where job needs are identified and the training required to fulfill those needs is specified (Chapter 39). These records should be updated periodically as training progresses.

Management must also assure that there is an adequate study plan for all studies and that personnel, resources, facilities, equipment, materials and methodologies are available, as scheduled, to accomplish that plan. In this regard all laboratory methodologies are to be incorporated into the standard operating procedures, which are deemed to be adequate to assure data quality and integrity. Further guidance is given in Chapter 16.

Finally, management must provide orderly archives for the proper storage of data, documentation, samples, and specimens that result from laboratory studies (see Chapter 36). This has to be given a high priority, since the lasting proof of study validity is contained in the materials derived from the study and stored in the archives.

It is usual for management to describe all responsibilities in a policy document as exemplified by the specimen included as Figure 1.

There is no question that management are ultimately responsible for the quality and integrity of the studies done in their laboratories. However, management must in turn delegate responsibility for quality to line managers, study directors, scientists, supervisors and technicians in proportion to the responsibility each has for subordinates and specific work activities.

### 13.3 STUDY DIRECTOR RESPONSIBILITIES

GLP mandates that the study director has a primary responsibility in assuring data quality and integrity, and in conducting a study to meet regulatory requirements. The study director should be a professional of appropriate education, training and experience, and be responsible for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of study results. This individual, who represents the single point of study control, is responsible for the following:

- Establishing and gaining approval of a study plan having clear objectives and adequate means to achieve the objectives.
- Implementing and monitoring procedures to ensure that the study plan and any amendments are followed.
- Assuring that all experimental data, including unanticipated responses to the test substance, are accurately, promptly and properly recorded.
- Assuring that unforeseen circumstances that may affect data quality and integrity are noted when they occur, and responsive corrective action is taken and documented.
- Determining that microbes, plants and animals used as test systems are as specified in the study plan.
- Amending the study plan in a timely fashion when it becomes necessary and assuring that the amendments are properly distributed to affected operational personnel.
- Evaluating the experimental results.

The management of the Laboratory will ensure work is carried out to the highest standard possible, in terms of scientific practice and that all research and development work is conducted in accordance with the Principles of Good Laboratory Practice (GLP).

These criteria can be met by:

- All *experiments* being properly planned and performed
- All *procedures* being from recognised SOPs and validated
- All *equipment and devices* being serviced and calibrated (where relevant) regularly and fully functional
- All *test systems and materials* being used are from accredited suppliers
- All *results* are correctly recorded, analysed, checked and reported

To ensure that this system is capable of operation a system of GLP has been implemented which will be audited on a regular basis.

#### *Scope of GLP*

All departments that are required to work to GLP will ensure that all aspects of their research and development will comply with the requirements. How this can be carried out can only be brought about by discussions between departmental heads, the QA Manager and the Director of Laboratory. Also, such matters as to the nature of the work, staff skills and experience must be taken in to account.

Where work is undertaken to satisfy regulatory statutory requirements for International Agencies, the Management will aim to comply with these principles in so far as they are practicable and in conformity with current laws and practices of the country.

No action will be allowed that contravenes the Health and Safety practices of those governing the use of laboratory animals.

#### *Operation of GLP*

The Management will assume responsibility for the definition of GLP in accordance with the current Principle applicable to the country. By meetings and information dissemination, the staff will be made aware of the requirements, and of their own responsibility. This action will be brought about by senior management and delegated where necessary.

It will be the responsibility of staff to familiarise themselves with the Policy, relevant SOPs and associated documentation, and to comply with the rules and regulations therein. Likewise, any department specific requirements will be identified by the department head who will ensure they are carried out in conjunction with the above.

#### *GLP inspection*

It is with full management backing that the relevant government inspectors will be allowed to carry out their duties to ensure full compliance with GLP is maintained. The company will make available to them any information relevant to the study under review or the facilities in general. Any matters of a confidential matter will be dealt with by a company confidentiality agreement or the agency's 'commercial in confidence arrangements'.

#### *Responsibility of the Study Director*

The study director has total responsibility for the overall conduct of the study, its report and archiving of raw data. Full details are given in the OECD Principles of GLP.

#### *Management responsibilities*

Management accept their responsibilities for GLP as set out in the OECD Principles of GLP.

#### *Staff and QA responsibilities*

The responsibilities of staff for the execution of the study, the QAU for overall audit and assurance of management as in the validity and integrity of the study are those detailed in the OECD Principles of GLP.

Signed.....  
(Director of Laboratory)

Date.....

**Figure 1** Example of a company policy statement on good laboratory practice

- Preparing a final report which is complete and which accurately reflects the experimental findings.
- Assuring that all raw data, documentation, study plans, specimens and final reports are transferred to the archives at the conclusion of the study.

It is acknowledged that a study director cannot be a technical expert in all the scientific phases that occur in, and are required by, contemporary study plans. Nonetheless, the study director should determine whether the established experimental procedures are adequate to achieve the study objectives and that the resulting data are promptly and accurately recorded.

It is also recognised that a study director may not be capable of preparing each of the technical sections included in a final study report. In this case it is acceptable that other contributing scientists write sections for their phases of the study, so long as the sections contribute meaningfully to the total report. In addition, the study director should assure that the conclusions of the contributing scientists are reflected in the conclusions of the report.

Many laboratories facilitate the job of the study director by following standard operating procedures that cover the assigned duties. Accordingly, discrete procedures are directed to formal study-plan development and amendment, data collection, evaluation, and archiving, test system selection and use, and final report development and approval. Often organisational policies define working relationships between the study directors and laboratory area supervisors. Satisfactory interpersonal relationships are essential to the smooth functioning of a laboratory and for the conduct of quality work.

The role of the Principal Investigator in multi-site studies is given in Chapter 15.

### 13.4 STUDY STAFF RESPONSIBILITIES

As mentioned, all personnel are responsible for assuring study quality. Quality cannot be added into a study at the time of preparation of the final report. Quality is built into a study from the point of study inception to the point of signature of a final report. Management may dictate quality, the study director may request quality and the quality-assurance unit may inspect quality, but organisational personnel actually assure quality by

- exercising diligence in the performance of assigned duties;
- maintaining the required level of proficiency;
- exercising judgement in reacting to unforeseen circumstances;
- knowing when to seek advice;
- reporting any illness that may affect the proper conduct of duties or the health of the test system;
- wearing, and changing, as necessary, any required protective clothing;
- taking necessary sanitation and personal health precautions;
- keeping accurate records;
- requesting necessary training;
- being honest;
- knowing applicable guidelines, rules and regulations that affect their work;
- being motivated.

By following these requirements the staff will contribute significantly to the study quality and ultimately the company's success. It is now appreciated that the GLP concept has value because it has formalised the experimental process by requiring the preparation of a detailed, complete study plan that comports with contemporary scientific criteria and that leads to the achievement of the objectives. Along with the study plan, GLP requires comprehensive standard operating

procedures that are clear and understood by personnel. The study plan and the standard operating procedures provide a set of documentation to demonstrate that the study was conducted properly, and that the reported findings are supported by the experimental observations. However, a system of plans, records, and procedures, is not sufficient to ensure the conduct of a high-quality study. This requires the presence of a trained, motivated work-force and an enlightened work environment. GLP assumes that personnel in a laboratory setting are self-motivated to do a good job. Quality work accrues therefore when personnel are trained in their specific duties, have adequate equipment and supplies, receive complete and clear instructions and know what is expected of them. In addition, personnel should be aware of their role within the organisation and of the value of their contribution to the company's goals.

### 13.5 QUALITY ASSURANCE RESPONSIBILITIES

GLP defines QA as the formal arrangements for assuring management that the facilities, equipment, personnel, methods, procedures and documentation conform to GLP requirements. GLP places only a single restriction on management's prerogative to organise and direct laboratory personnel as it sees fit. There must be an organisational and a functional separation between those individuals who conduct a study and those who perform quality-assurance duties. This restriction is based on the belief that quality-assurance personnel must act in a dispassionate, candid manner, so that there is no real, or perceived, bias in their work.

For each study QA need to determine whether it is in compliance with the study plan, relevant operating procedures and whether it conforms to GLP requirements. QA often use checklists as an aide memoir for each specific type of inspection. These are also invaluable when training new staff and they help reduce the risk of omissions due to human error. However, the checklists must be supplemented by intellectual input which repeatedly asks questions that tests the systems, measures quality, requires validation and judges any problem uncovered on the basis of impact on the study and frequency or probability of recurrence.

QA must therefore be both a systematic and an intellectual exercise, and will often also interact with the development phase of studies, methods of analysis, computer systems or other systems of work. To use the definition in the Guide to Good Pharmaceutical Manufacturing Practice (see Chapter 26), 'Quality Assurance is the sum total of the organised arrangements made with the object of ensuring that products will be of the quality required by their intended use'.

Quality considerations during the design and development of any system are the responsibility of the project manager who must be aware of what GLP requires from the finished product, but the extent to which QA should participate is a matter for local policy. It is not mandated by GLP requirements. This decision should be reached after considering the complexity of the project and the extent to which GLP compliance can be satisfactorily determined at the end of the development phase.

#### 13.5.1 The Quality Assurance Unit

The quality assurance unit (QAU) comprises the person or persons appointed by management to implement the QA programme, and who must be entirely independent of the personnel engaged in the study being monitored. Although GLP requirements permit a QAU establishment of one person, the consequences of this will mean that the QA programme will be readily compromised in the event of unforeseen absence during a critical phase of a study. There must in such circumstances be some contingency plan for combining QA work with other duties, provided that does not include responsibility of conducting any part of the study being monitored.

The main responsibility of the QAU is to develop, implement, and conduct procedures in Table 1. A thorough knowledge of GLP requirements is essential and the QAU should establish

**Table 1** *Responsibilities of the QA unit*

- 
- Establishment and maintenance of a master schedule sheet
  - Maintenance of copies of approved study plans and all amendments
  - Inspection of the operational phases of a study
  - Inspection of experimental processes
  - Inspection of study facilities
  - Auditing records
  - Auditing final reports
  - Making scheduled and ad hoc reports to management and to the study director
  - Monitoring actions taken in response to QA reports
  - Preparing a statement of QA inspectional activity for each study
  - Training organisational personnel in regulatory requirements
  - Acting as the laboratory contact point for regulatory and other inspections
  - Maintaining records of QA activities
- 

itself as the recognised source of advice on all matters of GLP interpretation and quality. This will not be achieved solely through the conduct of study and facility inspections and final report audits. The QAU should actively provide an advisory service, assisting with training of new scientific and technical staff as discussed in Chapter 38, participating in project team and departmental meetings when GLP matters are discussed, and holding direct discussions with study directors, departmental managers and scientific staff.

### 13.5.2 QA Staffing

A survey<sup>2</sup> of QA units suggested that 75% of QAU staff were recruited from within the company, most with a scientific background/degree, and the mean ratio of QA personnel to support scientific staff was 1:30.

In addition to recording management information such as financial data, man-hours worked, work throughput (study inspections, report audits, *etc.*) QA must allocate time for performing other tasks such as provision of an advisory service, external visits, supervisory and management duties, development of company or departmental procedures, professional development and training.

The level of staffing is a matter of local policy. Once a standard reporting scheme has been established, it provides a rational means for monitoring staff levels and, when necessary, for adjusting staffing levels or reviewing responsibilities so as to provide optimum service.

The QA officer requires to have a combination of technical and scientific experience, knowledge of GLP requirements and personal skills. Attributes for the ideal QA professional, are summarised in Table 2.<sup>3</sup> Such criteria can be applied as appropriate to the selection of new staff. However, few, if any, new or existing staff will possess all these desired attributes, and it will be necessary to enlarge and develop the skills base.

### 13.5.3 Training of QA Staff and Maintaining Training Records

Clearly all staff must possess sufficient scientific or technical background to understand technical SOPs, handle calculations and routine statistics, and use computers, as well as having some of the personal and communication skills required for QA work. Training programs for new staff must be tailored to individual needs and will depend on previous experience of working in a GLP

**Table 2** *Attributes of the QA professional*

Technical and scientific skills	Relevant laboratory experience and a scientific qualification Numeracy Computer literacy Ability to absorb technical information rapidly Questioning approach
Interpersonal skills	Analytical approach to problem-solving Effective team member Diplomatic approach Good listener
Communication skills	Good speaker Ability to instruct and train others Confident and enthusiastic Persuasive, a good negotiator
Personal qualities	Integrity Initiative and common sense Sense of humour Perseverance and determination Sense of perspective and judgement Resilience – thick skin
Management skills	Good at planning Forward looking, visionary Enthusiastic Ability to delegate Ability to decide and concentrate on priorities Sense of time and urgency

environment within or outside the company. All new staff must, however, initially attain an acceptable level of proficiency in having:

- A thorough knowledge of GLP principles.
- Familiarity with QAU procedures.
- A knowledge of the organisation and procedures in the areas to be monitored.

As discussed in Chapter 38 much of the training will be given by existing staff on a 1:1 basis which may be supplemented by supervised projects to encourage initiative, establish links with key departments and develop a thorough understanding of GLP requirements. Systematic training in QAU procedures is usually achieved by working alongside an experienced member of the QAU, the order in which procedures are undertaken being determined by the flow of work through the department. Proficiency will normally be assessed in two stages: initially the ability to carry out procedures alone but with reports being discussed with and approved by a supervisor, and subsequently the full authority to carry out procedures and report findings.

GLP requires individual training records to be maintained for all staff. Much training is relatively informal, which makes the record all the more important, ensuring proficiency is properly assessed and that clear authorisation to perform specific tasks exists. Proficiency in a particular procedure should be assessed by a supervisor/manager, and achievement of a satisfactory standard of work confirmed by dating and signing the training record. The training record should list all the topics which are to be covered, thus providing an immediate record of training and assessment still to be undertaken. Many companies will have their own graduate-training schemes, with courses to help develop interpersonal and oral and written communication skills, and provide an introduction to management. External training may also be useful, particularly for the small QAU, as specialised courses, which provide an opportunity for interaction and exchange of ideas between QAU staff,



are available. Professional development may be encouraged by attendance at, and participation in, relevant conferences and symposia.

### 13.5.4 QA Procedures

GLP also requires that the QAU shall have written SOPs, including those in Table 3, and elsewhere in the book. In many facilities the use of computers is an integral part of the conduct of studies, and these require specialised audit and inspection techniques, which are discussed in Chapter 37.

*13.5.4.1 QAU Aims, Scope and Organisation.* The aims will specify the standards to which the facility operates and with which the QAU seeks to monitor compliance. The completion of Memoranda of Understanding between the UK competent authority and various other monitoring agencies has ensured that the UK requirements take precedence within the United Kingdom. Residual uncertainty concerning specific requirements of foreign-product licensing agencies may, however, result in companies continuing to operate to combine standards.

The scope of the QAU GLP internal-monitoring activities is determined by the current requirements of licensing authorities and the company's perception of what might be required in the future, bearing in mind that compounds under current investigation will probably not reach marketing application for 5–10 years or more. Although new requirements will not be applied retrospectively, it is important that no situation adversely affecting confidence in the studies being submitted will arise. Only those studies intended for regulatory submission need to be monitored by the QAU; range-finding and other exploratory and development studies, although generally conducted to GLP standards, will not normally be subject to regular monitoring.

When a company purchases services or materials, whether it be a complete study, pathology, histology or analytical support services, animals, feed or bedding, *etc.* the supplier will be responsible for meeting the agreed quality standards. The selection of sources of supply and

**Table 3** *Quality assurance unit standard operating procedures*

- 
- Quality Assurance Unit aims, scope and organisation
  - Preparation and approval of QAU SOPs
  - Selection and training of QAU staff
  - QAU staff records
  - Review/approval of facility SOPs
  - Protocol (study plan) approval
  - Planning, recording and reporting inspections
  - Conducting study phase inspections
  - Conducting study data inspections
  - Conducting process inspections
  - Conducting facility and archive inspection
  - Inspection of staff-training records
  - Computer system development and validation
  - Computer data audits
  - Computer system and facility inspection
  - Final report audits
  - Preparing QA statements
  - Inspecting contract laboratories
  - Supplier inspections – animals, feed, bedding
-

monitoring of the supplier to ensure systems are adequate to meet the agreed quality standards is the responsibility of the sponsor/purchaser.

When complete studies are contracted out to other laboratories, it should be the responsibility of the sponsor's QAU to determine by periodic visits that the contractor's facility, procedures and monitoring systems are generally in compliance with GLP requirements. The frequency of monitoring visits will depend on the nature of the study and the contract laboratory's demonstrated capability. The sponsor is not required to inspect individual phases except in circumstances where a procedure may be contracted to a specialist laboratory, which does not have its own QAU. In such cases the contractor's laboratory should be considered as an extension of the sponsor's facility and subjected to equivalent requirements and monitoring procedures (see also Chapter 19).

The health and quality of animals and the quality of feed and bedding must also be assured, but the selection and inspection of suppliers is not a mandated QAU responsibility. This is, however, an area where the experience of the QAU and other specialists can usefully combine, and it is recommended that the inspection of suppliers should be within the scope of the QAU's responsibilities.

Relevant organograms should show the structure within the QAU and the position of the QAU within the company organisation, with member(s) of the board having responsibility for quality matters. Job descriptions should also be provided, recording the main duties and responsibilities for each post within the QAU.

*13.5.4.2 Review/Approval of Facility Standard Operating Procedures (SOPs).* The UK Compliance Program indicates that the QAU will be asked to describe and document their part played in the review of SOPs. It is the responsibility of each department to maintain up-to-date SOPs, but with hundreds of SOPs in a facility it becomes a difficult situation to monitor unless procedures are reviewed regularly and systematically, as mentioned in Chapter 16.

Facility SOPs need to be available for reference during protocol approval and final report audits, and the QAU should hold files of all SOPs, together with authorised records of issue and review dates. Although it is not a mandated responsibility of the QAU to approve new or revised facility SOPs, this is considered a valuable exercise. It ensures that equipment, methods and materials do not change without the knowledge of the QAU, and the reviewer will check for consistency of procedures between departments and clarity of styles, freedom from ambiguity and general compliance with GLP principles.

*13.5.4.3 Planning, Recording and Reporting Inspections.* The careful planning and timely execution of inspections are critical to the success of the QAU program. The selection of phases to be inspected, the frequency of process and facility inspections and reporting of findings are discussed in Chapter 17. Once planned, the proposed date must be entered into a manual or electronic diary system which allows facilities for revision should the scheduled date of any study phase change. There is no single favoured planning system, but many QAUs, for reasons of efficiency and improved-management information, will use computer systems to combine preparation of the master schedule (Chapter 14), planning, recording and reporting inspections and constructing the QA statement (see later).

The report of inspection findings must be sent promptly to the study director, or, for process and facility inspections, to the appropriate departmental manager/supervisor. A copy must also be sent to management. It is usual for the report to have a reply section for the recipient to record any actions that are necessary, sign to confirm receipt, and return to the QAU. Significant findings, which may affect the integrity of the study, must be discussed immediately with the study director, and be reported to management, before the written report is prepared.

It is essential that agreement is reached between the QAU and the study director concerning the appropriate actions to be taken, and these must be followed up to the satisfaction of the QAU.

In the event of any unresolved difference of opinion the matter should be referred to senior management for consideration and final decision.

The copy of the completed QA report signed by the study director is retained in the QAU study file. This is confidential and does not have to be made available to any government inspector, thus preserving the frank lines of communication between the QAU and study directors. The report is the confirmation of what, if anything, was found and what actions were taken to correct any deviation. These reports must be retained by the QAU. If a regulatory authority requests a study audit some years later, questions may arise during the review of raw data. Staff may have changed during this time and memories will certainly fade. The inspection reports for that study will provide information to the QAU which, although confidential, may assist in providing answers, and will certainly confirm what activities the QAU carried out during the conduct of that study.

### 13.5.5 The QA Statement

The GLPs are specific in defining how QAUs achieve their monitoring function. This is by way of conducting in-life critical phase inspections, facility inspections, data reviews and ultimately an audit of the final report. Details of these QA functions are dealt with elsewhere in this book. The keeping of careful records of all QA activities cannot be over emphasised.<sup>4</sup>

The last phase of a study is the compilation and production of the final report. In many instances the final report is the company's product. It is most certainly the combined finished product of all the many contributors, and consists of information presented, for careful evaluation, to an agency responsible for reaching an accurate decision regarding the safety of the compound that has been tested. The QAU audit of the final report therefore has very special implications. The document must be carefully reviewed for completeness against the GLP-content requirements, accuracy of reporting, cross-referencing of all supporting documentation and raw data, statistical information, dates and time scales, dosage and regimen, *etc.* It follows that after audit the report should again be reviewed by the QAU to confirm that any amendments or corrections have been accurately effected.

Section II 2.2.1.f of the OECD guideline states that QA will:

*Prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data*

Other legislation has a similar requirement, although identification of inspection of study phases is not mandated, though certainly contract laboratories may find that it is a requirement of some of their sponsors. The Statement will record the date the final report was audited.

It is not always practicable to inspect all phases of all short-term tests – for logistical reasons as mentioned in Chapter 17. An alternative statement is therefore often used, stating that the study type reported involved frequent inspection of similar or identical procedures and that procedural inspections were made by the QAU of critical processes relevant to the study from at least one study selected at random. This method should ensure that each study is inspected at least once, and each phase seen, though from different studies.

Additionally it should be stated that, as far as can be reasonably established, the methods described and the results incorporated in the report accurately reflect the raw data produced during the study. The statement should be signed and dated by the Head of QA. It is this statement alone which says to the reader(s) of the report that, in compliance with GLP, the study has been monitored from start to finish, and that the report has been duly audited.

As with all GLP requirements the inclusion of the QAU statement in the final report is not an optional extra – something which is nice to have – it is a must. A final report will not be accepted without this statement. Consequently, the issue of this statement places a very heavy responsibility on the QAU and places a further emphasis on the importance given by the authorities to the adequate and consistent monitoring of studies by a properly staffed QAU. It also highlights the fact that QAUs can withhold the statement until the report is, in all its aspects, formally and finally approved. By definition this means that any and all areas of non-compliance, any discrepancies or deficiencies, must have been not only satisfactorily documented and recorded and suitably addressed but also fully reported. Any areas of non-compliance that may have occurred during the study must be duly reported and explained. Additionally, the QAU's statement should make reference to such matters. Major areas of non-compliance, which could result in study termination and rescheduling, should have been dealt with before the final report stage.

#### QUALITY ASSURANCE STATEMENT

Study reference number:

Study title:

Test substance:

In compliance with the Principles of Good Laboratory Practice this study has been inspected, and this report audited by the Quality Assurance Unit. As far as can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in writing to the study director and to management.

The dates of such inspections and of the report audit are given below:

Date	inspection/audit	Date of report to management and study director

Signature:.....

Date: .....

(Name) .....(Head of Quality Assurance)

**Figure 2** Example of QA statement – 1

Clearly, a QAU can only provide such a statement for those studies, or parts of a study, for which it has provided GLP monitoring. When work is contracted, or subcontracted out, then the QAU of the relevant facility should provide information concerning the work for which it was responsible. Clearly, the QAU statement cannot be seen as an absolute guarantee of scientific perfection or quality. It is, however, a clear and formal indication that GLP compliance has been taken seriously and that every responsible step has been taken to produce an accurate, quality report that reflects quality raw data generated during a study which has been conducted in compliance with GLP.

The GLPs do not specify the actual design and wording of this statement; consequently it varies from company to company, and statements will, like the GLPs themselves, be similar but not identical. Some examples are provided at the end of this chapter Figures 2–6. Figure 6 provides the minimum requirements of a QA SOP on QA statements.

### 13.5.6 Monitoring the Quality Assurance Unit

Management has responsibility for quality, for the appointment of the QAU manager and for monitoring performance of the QAU. By receiving reports of all inspections, management is aware

#### QUALITY ASSURANCE STATEMENT

Study number:

Inspections were made by the Quality Assurance Unit of the various phases of the study described in this report. The dates on which the inspections were made and the dates on which the findings were reported to the study director and to the facility management are given below:

Date of inspection	Date of reporting
--------------------	-------------------

This report has been audited by the Quality Assurance Unit. It is considered to be an accurate description of the procedures and practices followed during the course of the study and an accurate presentation of the findings.

Signature:..... Date:.....

(Name) .....(Head of Quality Assurance Unit)

**Figure 3** Example of QA statement – 2

QUALITY ASSURANCE STATEMENT

This study (Study number) has been regularly monitored by the Quality Assurance Unit by way of periodic inspections as required by Good Laboratory Practice Regulations. The dates of these inspections and of the subsequent reports to management are listed here:

<u>Date of inspection</u>	<u>Date of report to management</u>
---------------------------	-------------------------------------

---

This report has been audited by the Quality Assurance Unit and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of report audit:

Signature:.....	Date:
Name .....(Head of Quality Assurance)	

**Figure 4** Example of QA statement – 3

of the interface between the QAU directors and line managers, and will expect to see that valid and useful observations are being made and necessary actions are being agreed in a positive manner.

It is, however, quite proper that the inspectors should be inspected. But who should do the inspection? Some companies will have corporate audit teams, while others with more than one QAU may arrange for one unit to audit another. There are also a number of consultants well experienced to carry out such a task. Whatever system is used, the audit must be carried out objectively to be effective and the auditor must have experience of the systems in use and the standards that are required. There is no mandate for any one system of internal audit in GLP requirements, and management, which takes the ultimate responsibility for the quality of studies, retains the right to choose its own style of control.

*13.5.6.1 Inspection by Government Agencies.* Compliance with GLP requirements must be a continuous activity, and special preparation for an inspection by a government agency should not

### QUALITY ASSURANCE STATEMENT

Study number:

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

At the time of this study procedure-based inspections were made by the Quality Assurance Unit of critical phases and procedures relevant to this type of study. For the inspection of any given procedure studies were selected at random. All such inspections were reported promptly to the relevant study director(s) and to facility management.

This study was inspected on:.....

This report has been audited by the Quality Assurance Unit and is considered to be an accurate description of the procedures and practices used for such studies and an accurate reflection of the raw data.

Date of audit:

Signature:.....

Date:.....

Name .....(Head of Quality Assurance)

**Figure 5** *Example of QA statement – 4*

be necessary. Some arrangements, however, have to be made to ensure that inspectors have access to sufficient senior staff. The QAU provides the main link between inspectors and facility staff, and the QAU manager or deputy should be available throughout to accompany inspectors at all times.

In larger facilities inspectors may wish to go into more than one area simultaneously, which will impose additional demands on QAU resources. The first part of the inspection will normally be spent with the QAU reviewing QAU procedures and establishing an approximate program for the remainder of the inspection. If it is the first inspection of the facility, an opening meeting should be arranged to give senior management an opportunity to provide a summary of the nature of the work undertaken, the company organisation, and the management policy towards quality and GLP compliance. The inspector(s) will wish to review one or more studies selected from the archive, and accommodation should therefore be made available in a suitable quiet office.

During the facility inspection the inspector will want to see normal work in progress, and will probably question a selection of staff about local procedures and the tasks they are performing. The departmental manager or deputy should normally be present to monitor the course of the



STANDARD OPERATING PROCEDURE		Number
Title:	The Quality Assurance Statement	
Compiled by:		
Checked by:		
	Issue number:	
Authorized by:		
	Revision number:	
Date of issue:		
	Supersedes:	
NOTE:	This Standard Operating Procedures should be read in conjunction with SOP Number which details The Quality Assurance Unit's procedures in respect of the auditing of study reports.	
1.0	When the QAU's audit of the study report is completed, its findings are reported, in writing, to the study director for comment and /or action, and to management for information and action if necessary.	
2.0	When such action as may have been required is effected, the corrected / changed report is subjected to further checking by the QAU.	
3.0	When the report is finally considered to be satisfactory, the Quality Assurance Manager will sign the Quality Assurance Statement for inclusion in the final report as required by GLP.	

**Figure 6** Example of SOP on the QA statement

inspection in their department, and provide answers to any questions, which relate to policy or other management matters.

The QAU representative should ensure that all points raised during each day are accurately recorded, and these will normally be discussed with management at the end of each day so that any actions that may be required can be discussed and, if appropriate, simple measures put into effect immediately. On the last day of the inspection the inspector(s) will normally wish to present a summary of findings to management. It is important that, as far as practicable, relevant departmental managers and senior facility management are present at this exit meeting to ensure that the significance of any findings is fully appreciated and any misunderstandings discussed and resolved.

A facility where management is committed to quality will want to demonstrate compliance to the satisfaction of the government GLP Monitoring Unit, but will also wish to ensure that any recommendations made are soundly founded on GLP principles and, when implemented, will contribute to the reliability and integrity of work undertaken by the facility.

An inspection report, which will be sent subsequently, will be based on the points discussed at the exit meeting. A response will be required from management, confirming acceptance of the recommendations or giving reasons for any disagreement on fact. The actions being taken will be described, with approximate timescale to completion. The QAU should monitor progress to ensure that all actions agreed by management are implemented in a timely and satisfactory manner. The report and the lessons to be learned should also be put to good use by the QAU in discussions

and/or training sessions with all staff engaged in the conduct of studies. Competent authority inspections are discussed more fully in Chapter 12.

The importance of quality data generated from non-clinical laboratory studies must be of concern to managers, scientists and QA professionals both in industry and government. Their common activity therefore should be that of constantly reaching for excellence in order to achieve the common goal to produce safe and efficacious products.

## REFERENCES

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## CHAPTER 14

# The Master Schedule Index<sup>†</sup>

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### 14.1 DESCRIPTION AND AIMS

In order to keep track of the many ongoing activities in a toxicology laboratory, the good laboratory practice (GLP) Regulations require the Quality Assurance Unit (QAU) to maintain a copy of a master schedule sheet of all non-clinical laboratory studies conducted at a testing facility. This master schedule must be indexed by test article/substance, and contain the following elements (1) test system, (2) nature of study, (3) date the study was initiated, (4) current status of each study, (5) identity of the sponsor, (6) name of the study director and (7) status of the final report. While not a requirement of GCRP scheduling, it helps to ensure the most effective use of QA time in performing audits and inspection in the clinical trials area.

Although it is not specifically stated in the regulations, any of the above items may be encoded in order to protect sponsor confidentiality to shorten the master schedule, to interface it more readily with other facility schedules or for other administrative reasons. For example, instead of providing the sponsor name and test article/substance on the master schedule, a unique identification code encompassing this information may be assigned.

The content and format of the master schedule should be determined by the needs and capabilities of each particular facility, as well as by regulatory mandate. For example, a facility which conducts a few non-clinical studies in a given year may require only one spread sheet, issued monthly, and containing only information required by GLPs. Another facility, with many studies in progress, may opt to issue a separate sheet for each study or to issue a schedule which contains more information than is required by GLPs, so that the master schedule interfaces more readily with other facility schedules. Whatever form the master schedule takes, it should serve the QAU, the research team and management as a useful scheduling and reference tool. A master schedule generated and maintained merely to fulfil regulatory requirements is a tiresome, time-wasting administrative burden.

### 14.2 MAIN ELEMENTS – CONTENT AND FORMAT

Two basic elements of the master schedule are its contents and its format: the former usually determines the latter.

GLP regulations explicitly state the minimal contents required in all master schedules. These are listed and described below:

- (i) *Test article/substance*: The master schedule, according to the regulations, must be indexed by test article/substance. While some facilities prefer to include the full name of the test

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<sup>†</sup>This chapter was felt by the Editor to be of significant importance and taken from *Good Laboratory and Clinical Practices*, P.A. Carson and N.J. Dent (eds), Heinemann-Newnes, 1990.

article/substance, others prefer that this information remain confidential and use a code for identification. Naturally a key to any code used in the master schedule should be available to the QAU and to other relevant departments. Test 'article' is the preferred FDA terminology; test 'substance' is the preferred EPA terminology.

- (ii) *Test system*: This refers to the animal, plant, micro-organism or subparts thereof which are administered the test or control article/substance. It also refers to any subjects not administered either the test or control article/substance which are to be used as a basis for comparison with treated groups. This is usually stated simply on the master schedule, for example, B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> Mice.
- (iii) *Nature of study*: This usually requires a brief descriptive statement of the kind of project conducted, including route of exposure and additional, significant parameters: for example, 'Multi-generation, with behaviour, gavage'. Some master schedules may include the entire study purpose when recording this parameter: for example, 'To determine the sensitising potential of ABC when applied dermally for 10 consecutive days to female B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> Mice'.
- (iv) *Date study was initiated*: GLP regulations define study initiation as the date when the protocol is signed by the study director. If this date is not available at the time the study is entered into the master schedule, it can be replaced by a footnote denoting that the study director has not yet signed the protocol. For example, it may not be possible for a master schedule issued on 1 March to include the starting date of a study starting on 29 March. The protocol for that study may still be in 'review status' on 1 March and may not be signed until 28 March.
- (v) *Current status of each study*: This may be very simply stated by providing descriptions and dates for the various parameters (acclimated 02/10/88-02/ 21/88, administered test article 12/22/88-12/22/89, etc.) or by plotting out the various study phases as in Table 1. Some master schedules do not provide any dates for this portion; instead, they only state 'in-life' or 'final report' to reflect the current study phase. Sometimes the study protocol is referenced for dates.

**Table 1** Master schedule which plots study phases

MASTER SCHEDULE – MARCH 1989							
Study and director	Start/end	Type	Mar. '89	Apr. '89	May '89	Jun. '89	Jul. '89
001-1	02/17/89	DRAGON					
DR. X	07/08/89	SEG II, ORAL	A(11/29) +I(30xxxxxx3)	+T(5/21) +C(28xxxxxxx4)		----- F(8)	
002-2	01/30/87	MAMMOTH					
DR. L	04/06/89	PILOT, I.V.		----- F(6)			

**SAMPLE KEY**

A = acclimation

I = insemination

T = test article administration

C = Caesarean-sectioning

F = final report

xxx = in-life phase

-- = post-mortem phase

- (vi) *Identity of the sponsor*: For studies with out-of-house sponsors, the sponsor identity is almost always encoded for confidentiality. Sometimes one set of numbers is used to encode not only sponsor identity, but also the test article/substance and the test system.
- (vii) *Name of the study director*: This requirement is self evident.
- (viii) *Status of the final report*: Most master schedules will minimally include the study completion date to fulfil this requirement. The study completion date is defined by the GLPs as the date the final report is signed by the study director. The master schedule may also contain information on whether the final report is in the process of being audited by the QAU or whether it has been archived.

An example of a master schedule which provides minimal information is provided in Figure 1. Such schedules can be profitably used to accomplish the following:

- (i) To provide management, study personnel and the QAU with a synopsis of ongoing work.
- (ii) To provide agency investigators and management with a picture of each study director's burden.
- (iii) To provide input for trend evaluation and project planning.
- (iv) To serve as an historical record.
- (v) To serve as an index for archiving purposes.
- (vi) To alert personnel to GLP work in progress.

*NON-CLINICAL QUALITY ASSURANCE MASTER SCHEDULE  
GLP REGULATED STUDIES 12/01/87 TO 12/01/88*

*TEST ARTICLE: PPP*

STUDY IDENTIFICATION NUMBER: 01  
 TEST SYSTEM: Little Dinosaur  
 TITLE: The toxic and carcinogenic effect of WWW administered in  
 feed to Little Dinosaurs for 2 years  
 STUDY DIRECTOR: Dr A.  
 INITIATION DATE: 02/20/88  
 STATUS OF STUDY: In-life  
 STATUS OF FINAL REPORT: Not yet applicable

*TEST ARTICLE: DDD*

STUDY IDENTIFICATION NUMBER: 02  
 TEST SYSTEM: Big Dinosaur  
 TITLE: Reproductive and behavioural evaluation of BBB when admi-  
 nistered to Big Dinosaurs in drinking water during cohabitation  
 STUDY DIRECTOR: Dr B.  
 INITIATION DATE: 02/20/90  
 STATUS OF STUDY: Protocol only  
 STATUS OF FINAL REPORT: Not yet applicable

*TEST ARTICLE: HHH*

STUDY IDENTIFICATION NUMBER: 03  
 TEST SYSTEM: Medium Dinosaur  
 TITLE: Subchronic inhalation toxicology evaluation of Medium Dino-  
 saurs exposed to MMM for 6 hours daily for 90 days  
 STUDY DIRECTOR: Dr C.  
 INITIATION DATE: 06/20/87  
 STATUS OF STUDY: Completed  
 STATUS OF FINAL REPORT: Completed

**Figure 1** Master schedule with only GLP-mandated information, list format

The master schedule can also serve as a prompter for the interface with other facility schedules, especially QAU inspection/audit plans. Master schedules which are used in this way usually include more information than is mandated by the GLPs. They may include information about (1) the designated regulatory agency, (2) where the study will be conducted (on or off site, name of contract laboratory, building and room location), (3) number of study subjects used, (4) draft report status, (5) archived status of final report and tissues, specimens, slides and blocks, (6) study cancellation date (if applicable) and even (7) summarized study results. An example of a master schedule which includes some of this information is provided in Table 2.

Including too much information in a master schedule can of course be counterproductive. Frequently, it is more sensible to interface the master schedule with other types of schedules or to use the master schedule as a prompter for other information. Many QAUs use the master schedule to reflect the status of their own critical phase inspection and data/report audit schedules. Other QAUs incorporate the critical phase inspection schedule as part of the master schedule. Examples of these are provided in Figures 2 and 3.

### 14.3 TYPICAL STYLES AND DESIGN TECHNIQUES

The master schedule may be generated by hand (usually information is hand-entered on a prepared form as in Figure 3), by a personal computer calendar system (as in Figure 2), by some other sort of software graphic system (as in Table 1) or by a software package which interfaces with other facility systems (as in Figure 4). The schedule may be formatted so there is a separate page for each study (as in Figure 3) or so that all studies are on a summary type schedule (as in Table 1 or Figure 4). Some facilities generate both an individual (by study) and a summary master schedule. In addition the master schedule may be selectively generated, so that separate schedules exist for various categories of studies, that is on-site/off-site, GLP/non-GLP, FDA/EPA, *etc.*

The varying styles of master schedules presented in the various figures and tables in this chapter were chosen by the facilities utilising them on the basis of several considerations, the most fundamental of which was whether the schedule was to be designed merely to meet regulatory requirements or whether it was to function as a useful tool. Those facilities which utilise the schedule only to pass GLP inspections include only minimal information, update their schedules once monthly or less, and frequently never issue the master schedule except for GLP inspections or when the schedules are archived. Usually such master schedules do not interface with other schedules.

The most useful schedules are usually those which interface well with other schedules and are flexible, that is which can be manipulated and updated frequently to reflect changes in study status (progress from one phase to another, postponement, cancellation, addition of new parameters) or the addition of new studies to the facility agenda. Some of the most useful master schedules are generated from the same database used by research to process protocols and schedules, issue status reports and generate study reports. Usually such systems make it possible to sort the master schedule in a number of ways (test type, species, study director, regulatory intent, chronology, test article/substance, sponsor, *etc.*) and to use the master schedule as the basis for the QAU inspection/audit schedule. It is usually also possible to program the system to produce summary, monthly or more frequent master schedules as well as detailed printouts describing ongoing critical phases.

#### Maintenance

The GLP regulations state that the QAU is responsible for the maintenance, not generation or production, of the master schedule.<sup>3</sup> While most schedules are produced as well as maintained by the QAU, the master schedule may also be generated by the various departments in research, by GLP compliance groups within these departments, or by administrative personnel such as archivists or secretaries. In some facilities various departments within research all have input into the

**Table 2** Master schedule with more information than is mandated by GLPs, linear format

MASTER STUDY LIST FOR CARCINOGENICITY EVALUATIONS								
Protocol	Reg. agency	Test article/ substance	Species	Room	Start	Sacrifice	Report	Director and tech.
35-05	EPA (FIFRA)	PESTICIDE	UNICORN	BIG (7)	02/17/89	02/17/91	02/17/92	MERLIN & ARTHUR
								UNUSUAL
35-09	FDA	DIURETIC	MAMMOTH	VERY BIG (8)	03/01/89	03/01/99	12/01/99	HANZEL & GRETEL
								A MAMMOTH UNDERTAKING



MASTER SCHEDULE			
Short ID:	HHH		Test Article: Happyholdhen Test System: Unicorn
Protocol:	HHH-1		
Director:	Dr Z		
Sponsor:	Big Company	Initiation Date: 12/01/89	
PURPOSE:	To determine the sensitizing potential of HHH when applied dermally for 10 consecutive days to female unicorns.		
STATUS:	Protocol _____	In-life <input checked="" type="checkbox"/> X _____	Special Audits _____
	Data Audit _____	Final Report _____	Archived _____
MONDAY, 4 DECEMBER 1989		9:40AM	
1989 DECEMBER	DAILY	CALENDAR	
MON. 4	HHH-application/dosing	HHH-application/dosing	THU. 5
TUES. 5	HHH-application/dosing	HHH-application/dosing	FRI. 6
WED. 6	HHH-application/dosing	HHH-application/dosing	SAT. 7

**Figure 2** Master schedule generated in a personal computer. This master schedule contains a page for each study and generates a daily calendar reflecting scheduled critical phases

master schedule, which is then summarized by the QAU. This approach works very well with master schedules which are driven by the same computerised data or program base as other in-house schedules and protocols.

The master schedule is usually issued monthly, except in those facilities where it is never issued except for GLP inspections; such facilities depend on other schedules to prompt and track their work. However, even when the schedule is issued monthly, it is frequently updated on a weekly, daily or 'as required' basis.

The master schedule is a legally mandated document. As such, it should be archived on a regular basis in a secure area (fireproof). The master schedule is almost always reviewed by FDA/EPA investigators during inspections and is frequently used to select study records and activities to be audited/inspected. Thus retired master schedules which are stored on computer tapes, disks or other media must be accessible.

#### 14.4 STANDARD OPERATING PROCEDURE

A standard operating procedure (SOP) describing the master schedule should be maintained by every facility. This SOP should include information on:

- (i) Content.
- (ii) Format.
- (iii) Who generates, maintains, issues.

MASTER SCHEDULE			
Regulatory Intent	<b>EPA</b>	Study Number	<b>46</b>
Test Article(s)/Substance(s) <b>ZZTTTTDDDDAAA</b>			
Test System	<b>Sabre-toothed Tiger</b>	Study Director	<b>Dr Prehistoric</b>
Nature of Study <b>Chronic Carcinogenicity Study (Dosed Water) of</b>			
<b>Cavity Retarding Agent</b>			
Study initiation Date	<b>12/20/88</b>	In-life Termination Date	<b>03/01/90</b>
In-life Initiation Date	<b>03/01/89</b>	Study Completion Date	<b>07/15/90</b>
Prepared By	<b>Dr Prehistoric</b>	Date	<b>03/01/89</b>
Current Status			
<input checked="" type="checkbox"/> Acclimation	Initials <b>ZZZ</b>	Date	<b>01/01/89</b>
<input checked="" type="checkbox"/> In-life	Initials <b>FFF</b>	Date	<b>03/01/89</b>
<input type="checkbox"/> Post Mortem Pathology	Initials	Date	
<input type="checkbox"/> Report in Preparation	Initials	Date	
<input type="checkbox"/> Report in Review	Initials	Date	
<input type="checkbox"/> Report sent to Sponser	Initials	Date	
X - Lowest box checked = current study status      NA - Not applicable			
Comments {if applicable}: <b>No effect noted to date (06/02/89).</b>			

**Figure 3** Master schedule generated by hand, and containing one page for each study

MASTER LIST AS OF 01/01/89						
00-000-01	6 MO.	OT	160	RAT	JJB JJB ARR	
50, 25, 10, 0	MG/KG					
Started	Necropsied	Reviewed	Final	Audited	Issued	
10/12/1988	04/18/1989					
TEST ARTICLE: ANALGESIC						
00-000-02	SEG1-REPR.	OT	180	RAT	SWS SWS	
200, 100, 50, 0	MG/KG					
Started	Necropsied	Reviewed	Final	Audited	Issued	
06/23/1989	03/12/1989	12/30/1989				
TEST ARTICLE: ANTIBIOTIC						
00-00-03	EXPLOR.	OT	6	BEAGLE	JJB JJB WBM	
300, 0	MG/KG					
Started	Necropsied	Reviewed	Final	Audited	Issued	
02/22/1989						
TEST ARTICLE: ANTIVIRAL						

**Figure 4** Computer-generated master schedule which interfaces with other facility schedules

- (iv) Frequency.
- (v) Archiving.
- (vi) Key for abbreviations, codes. A sample SOP follows: Master Schedule Sample SOP.

### **Master Schedule SOP**

A master schedule for all studies conducted by XXX Research Labs, Inc., will be generated either by the Quality Assurance (QA) unit or by the research department on a monthly basis. The current master schedule will be maintained by and will be on file in the QA office. It will report the current status of each study. The following items will be included in each master schedule:

- (i) Month master schedule is issued.
- (ii) List of the studies assigned by number code (indicating sponsor and test article/substance) and a section containing the following information on the conduct of each study.
  - (a) Test system.
  - (b) Nature of the study.
  - (c) Dates of the initiation and the completion of study (initiation is defined as the date the protocol is signed by the study director; completion is defined as the date the final report is scheduled to be signed by the study director).
  - (d) Study director.
  - (e) Monthly calendar illustrating the current status of the study as well as the projected status of the study. A code will be used on the master schedule to describe the status of critical phases for each study.

Copies of each month's master schedule will be disseminated to the following personnel:

- Director of research.
- Department directors.
- Staff veterinarians.
- Group leaders.
- Senior scientists.
- Laboratory supervisors.
- All members of QA unit.
- Appropriate administrative personnel.

Original master schedules will be kept in an historical file by the QA unit.

## **14.5 CONCLUSION**

The content, design and maintenance of the non-clinical study master schedule is determined both by regulatory mandate and by the needs and capabilities of each facility. The schedule can be utilised simply to meet regulatory requirements or as an administrative tool which will assist all departments, including management, in the fundamental tasks of evaluating, planning and tracking.

## **FURTHER READING**

1. Food and Drug Administration, 'Good Laboratory Practice Regulations; Final Rule', *Federal Register*, Part VI, Friday, 4 September 1987.

2. Environmental Protection Agency (1983) 'Toxic Substances Control: Good Laboratory Practice Standards; Final Rule', *Federal Register*, Part III, Vol. 48, No. 230.
3. Environmental Protection Agency (1983), 'Pesticide Programs; Good Laboratory Practice Standards; Final Rule', *Federal Register*, Part IV, Vol. 48, No. 230. [Note that the Organisation for Economic Co-operation and Development's 'Final Report on the Group of Experts on Good Laboratory Practice' [(1982), (ISBN 92-64-12367-9)] does not contain a requirement for a master schedule.].
4. *Ibid.*, paragraph 58.3(i) (FDA); paragraph 792.3(p) (EPA,TOSCA); paragraph 160.3(p) (EPA, FIFRA).
5. *Ibid.*, paragraph 58.35(b.1) (FDA); paragraph 792.35(b.1) (EPA, TOSCA); paragraph 160.35(b.1) (EPA, FIFRA).



## CHAPTER 15

# Study Plans and Their Audits

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### 15.1 DEFINITION OF THE STUDY PLAN

OECD GLP Principles<sup>1</sup> and UK GLP Regulations<sup>2,3</sup> contain virtually identical definitions: “*Study plan* means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments”.

The first key point in this definition is that the plan is a document: it must therefore be in writing. The second point is that the plan is itself an instrument of definition: it is a description of the design, extent and intent of the piece of work. “The study” is defined by the content of the study plan. The final phrase introduces the concept that the plan, once defined, may be subject to controlled change.

It would be a useful addition to the definition to specify that the study plan should be agreed and authenticated. It will be seen in the following section that the prime purpose of the study plan is to help ensure that all participants in the study share a common understanding of the detailed intentions. Such common understanding is unlikely to be reached unless the participants have the opportunity to review the document in draft form, and raise for clarification any points of perceived ambiguity or technical difficulty. Such a process may result in the production of several versions of the plan so it will be necessary to identify the final version, agreed between all parties, by an authenticating signature. This avoids the possibility of confusion of an early version with the definitive version.

In some countries and institutes, the term “study protocol” is preferred to study plan and is the term in GCP (Chapter 2). These terms are synonymous within the context of GLP, but the OECD-preferred term is used throughout this chapter.

### 15.2 PURPOSE OF THE STUDY PLAN

It should be appreciated that a regulatory study is a complex operation often performed over a significant period of time, by a number of operatives and specialists working in disparate cultures. The duration of some studies implies that staff changes during the study will be inevitable. The potential for confusion or oversight is high, as evidenced in the early 1970s by the findings of the United States Food and Drug Administration (US FDA). Thus, the presence of a written and authenticated description of the study requirements was considered to assist with proper execution of the study by providing all participants with clear instructions for their roles.

This is the fundamental GLP purpose of the plan, but it may also serve as a basis for contractual agreement between study sponsors and testing institutions, and in the case of multi-site studies between test facilities and test sites. The importance of the plan to GLP as a principle, and to the

integrity of studies, should not be underestimated. It is the key controlling document for a study. It is the logical starting point for any assessment – by inspector, monitor or auditor – in the evaluation of a study. It is mentioned in no less than 52 places in UK GLP Regulations.<sup>2</sup>

### **15.3 RESPONSIBILITIES IN RESPECT OF THE STUDY PLAN**

Several individual and group responsibilities are defined in GLP. It is the responsibility of management to ensure that the Study Director authorises the plan and makes it available to the Quality Assurance (QA) personnel. It is the Study Director's responsibility to perform the above actions; to ensure that the plan and any amendments are available to technical staff; to ensure that it is followed; to assess any deviations from it and to transfer it to archives at the end of the study. It is the responsibility of technical staff to ensure that they have access to the plan and that they adhere to it.

Quality Assurance responsibilities in respect of the plan are to maintain the copies provided by the study director, to verify them for compliance and to monitor availability to and adherence by technical staff.

### **15.4 FORMAT OF THE STUDY PLAN**

The OECD GLP Principles list identifiers that must be provided, and topics that must be addressed in every study plan: these are discussed later in this chapter. Beyond this, the format and layout of the plan is at the discretion of the testing institution but at all times, the design of the document should facilitate ease of use. The purpose of the plan must be borne in mind, such that information therein is clearly and logically presented. Style of presentation inevitably will be formal and scientific, but the language chosen must be appropriate to the end-users who will range from senior experts to junior technicians. Tables, figures, appendices and summaries should be considered if they aid adherence to the instructions. For example when a discrete part of the study is the responsibility of a specialist in another organisation, the relevant requirements may be separated out into an appendix, to which the main text simply refers. Furthermore, it may not be helpful to burden the study plan with lengthy descriptions of common or standard procedures. This level of detail may be more appropriate to standard operating procedures (SOPs), to which the study plan may refer.

For some types of study the design may follow a published standard, such as one of the OECD Guidelines for the Testing of Chemicals. If a testing institution regularly performs many studies to such a standard design, it will aid proper and efficient compilation if the text of the study plan is held in a template file. Inserting the variables such as names and dates into the appropriate fields then completes the plan. Alternatively, the standard text may be provided as a controlled company document such that the study plan itself, perhaps reduced to a single page, contains just the variable information, reference to the controlled document and the approval. This structure is described as a “general study plan and study specific supplement” in the OECD GLP Principles: the concept is exemplified in Figure 1, which also illustrates the extent to which a GLP-compliant study plan may be reduced in volume.

### **15.5 REQUIRED CONTENT OF THE STUDY PLAN**

The references after the following section titles relate to Schedule 1, Part VIII of UK GLP.<sup>2</sup>

#### **15.5.1 Unique Identification (3.-(1))**

All study items, including the study plan, should carry an identifier that uniquely identifies the study. The form of identifier is not specified in GLPs: each test institute should design a system



<COMPANY NAME>

STUDY PLAN

STUDY NUMBER 2002/12345

<TEST ITEM>:  
ACUTE ORAL TOXICITY TEST TO HONEYBEES

TEST METHOD: In-house Procedure No. E-17, in compliance with EU  
Directive 67/548/EEC Annex V Test C.16

PROPOSED START DATE: 1 May 2002

PROPOSED COMPLETION: 28 June 2002

SPONSOR: General Chemical Co  
<Address>

TEST FACILITY: Company  
<Address>

DOSE LEVELS: To be documented in the study data following a preliminary  
toxicity test.

Study Plan Accepted: \_\_\_\_\_ (Study Director) \_\_\_\_\_ (Date)

**Figure 1** Example of a study-specific element to a general study plan meeting the basic requirements of GLP

appropriate to its work and culture, and document it in a SOP. It is thus possible that more than one institute may operate an identical system, but the combination of institute name and study identifier will be unique.

### 15.5.2 Descriptive Title (2.-(1) (a) (i))

The title should describe the type of study in a few phrases. If the type is standard and widely known, a few words may suffice; in other cases a medium-length sentence may be required. In most cases it is appropriate to incorporate the name of the test item in the study title.

### 15.5.3 Statement of Nature and Purpose (2.-(1) (a) (ii))

As with the title, the length of the introductory statement will vary with the degree of standardisation of the study design. A bespoke study to investigate a specific aspect of toxicology may require several paragraphs to set the scene and describe the aims of the work, while for a routine standard study it may be sufficient to state that it is designed to meet a published test guideline.

### 15.5.4 Identification of Test Item (2.-(1) (a) (iii))

Care is sometimes needed with this fairly obvious requirement. GLP offers various suggestions for identifiers (code, name, CAS number, biological parameters, *etc.*), which implies that any appropriate identifier is acceptable. Two considerations are paramount: that the identifier is sufficiently

detailed to allow unambiguous identification of the item intended for test, and that the identification on the study plan relates to the identifier given on the test item itself or on its container.

Many test items are adequately identified by name (Zinc phosphide, Intense Red VSD, 2,4-bis (4-methyl. . .), *etc.* Code numbers are acceptable substitutes (Experimental Substance ABC23456, Item MX-OP), although sponsors should resist the use of “Compound X” since such names rarely are, or remain, unique. For some studies, however, it is important to specify the lot or batch number of material to be tested, if the purpose is to determine properties of a specific batch or batches.

Particular care is required with test items to be supplied for test as a dilution. It must be absolutely clear whether the material is provided to the test institution neat (in which case the test item should be described as “ABC” for testing as a 20% dilution), or already diluted (“ABC 20% dilution”). Such a simple but fundamental error during preparation of the study plan would almost certainly invalidate any subsequent work on the study.

A few studies may involve the use of more than one test item. This is acceptable so long as all materials are identified in the study plan, and at the end of the work all the results are presented in a single final report.

#### **15.5.5 Reference Item (2.-(1) (a) (iv))**

If known active (positive) or inactive (control) reference items are appropriate to the study, against which the results from the test item are to be compared, they should be specified in the study plan. The purpose of this requirement is to preclude the possibility of adjusting the study outcome by retrospective selection of reference data. However, the use of reference items to generate facility-based background data on (say) the continuing sensitivity of the test procedure, is outside the scope of a specific study. This is discussed later.

#### **15.5.6 Sponsor (2.-(1) (b) (i))**

The name and address of the sponsor organisation should be given. Although correct identification of the sponsor is unlikely to be critical to the proper conduct of the study, it is a required element of the GLP study plan.

Issues can arise when the sponsoring organisation is a consortium or common-interest group, and has no single address. One of the constituent members generally acts as the point of contact, so the sponsor can be given as “the consortium care of the major contact at his normal business address”, but in other cases there is no option but to list the names and addresses of all the consortium members.

Clear understanding of the sponsor identity is needed when a testing institution takes on a package of work, but sub-contracts part of it. The subcontractor will have a contract with the primary testing institute, but that primary institute will not be the study sponsor, so the risks of conflicting definitions of Sponsor are high. It is important to reach an early agreement on this, since once the plan has been finalised any corrections may only be made by formal Amendment (see later).

#### **15.5.7 Test Facility and Test Sites (2.-(1) (b) (ii))**

The study plan must identify all test institutes involved in the study, and specify their roles. The simplest arrangement is for the work to be done within a single organisation, but significant numbers of studies involve multiple sites. In this situation, one company, usually the facility responsible for the bulk of the work and providing the Study Director, is generally identified as the Test Facility. Other institutes, usually performing a limited segment (phase) of the study and providing a principal investigator (PI) or Contributing Scientist, are generally identified as Test Sites. The definition of Test Facility and Test Site given in the OECD Principles may be confusing, so it is important to be unambiguous in the use of this terminology in the study plan.

In respect of Test Facility and Test Sites, the major points of concern when constructing a study plan are the following:

- The study plan should be used as the instrument by which any confusion relating to terminology of test facility and test sites is resolved.
- The study plan should be used as the instrument by which any potential confusion relating to roles of individuals or companies is precluded.
- The Study Director should be based at a location that facilitates full and proper completion of the Study Director's role. In extreme cases, this may be at a location at which none of the experimental work takes place but such an arrangement would require very careful justification to be credible.
- A Test Site that is not included in a national GLP monitoring programme cannot provide a PI, a GLP archive or a GLP QA function.

### **15.5.8 Study Director (2.-(1) (b) (iii))**

The study plan must identify the name and address of the Study Director. In complex multi-site studies it may be essential to specify the Study Director's business address overtly: in the other cases it may be implied that the address is that of the (sole or primary) test institute.

### **15.5.9 Principal Investigator (2.-(1) (b) (iv))**

When the Study Director for geographic or managerial reasons, will be unable to fulfil his/her duties in respect of one or more remote GLP-compliant phases of the study, a PI will be appointed at each site to assist the Study Director. All such PIs and their business locations must be identified on the study plan and their respective roles must be clear.

Note that the role of the PI is fundamental to the operation of a GLP multi-site study. Therefore, a PI can only be appointed at a GLP-compliant site. If a non-compliant site must be used for part of a GLP study, the key individual at the site should be styled "Contributing Scientist". In the United Kingdom the GLP-Monitoring Authority must be notified in advance of such intentions, and the main test facility must make arrangements for monitoring by management and QA. Alternatively, the claim of GLP compliance for the study must exclude the work done at the non-compliant site, and this intention should be explicitly stated in the study plan.

### **15.5.10 Approval (2.-(1) (c) (i))**

The study plan must be authorised by the dated signature of the Study Director, and this signature effectively puts the study into being and is recognised as the "study initiation date". Prior to signature the document has no GLP status and is simply a draft: once signed, the study officially exists and can only be terminated by completion of all the activities or by formal Amendment. This is the only signature mandatory under OECD GLP. The sponsor is required to approve the study but not expressly by signature on the plan – although this would be the most obvious mechanism in many cases. The study must not begin until the plan is authorised (*i.e.* the study-initiation date must not be later than the experimental start date).

It occasionally happens that a draft study plan undergoes a prolonged period of discussion before agreement on the content; then, when all is agreed and the study can be initiated, the allocated Study Director is not available to sign the plan, perhaps because of illness or holidays. No alternative authorisation is possible in the absence of the Study Director. Either, study authorisation awaits the return of the allocated Study Director or another individual is appointed as Study Director by management.

Principal investigators are required to show that they agree to perform their delegated phases of the study, but again the mechanism for this is not specified. Signature of the study plan is once more an obvious option, although consideration must be given to timing. It would not be appropriate for the Study Director to authorise the plan before the commitment of PIs was assured.

Where a General Study Plan is issued with a study-specific addendum (as exemplified in Figure 1), the study-specific addendum provides for the signature of the Study Director. In signing this addendum, the Study Director approves the use of the quoted general study plan on this specific study, so it is not necessary for the Study Director to approve the general study plan separately. Like SOPs that may be similarly referenced, the general study plan is most appropriately authorised by the management of the facility in which the standardised tests are done.

#### **15.5.11 Dates (2.-(1) (c) (ii))**

The proposed experimental start date and the proposed experimental completion date are required: the terms are defined in OECD Principles but may be subject to more specific interpretation by national GLP-Monitoring inspectors, or by individual company policy. Where these dates are known accurately they should be stated to the day. If appropriate, additional dates may be included (for example, in a chronic multidisciplinary study in which a clear, advance, agreed statement of schedule is necessary to proper operation of interfaces between the various specialities).

The scheduling of acute, single-discipline studies may be less predictable. Such studies are often terminated by endpoint, not by date: so that the completion of one study will affect the availability of resource for the start of the next. Under these circumstances, it seems reasonable to define the start and end dates to the month rather than the day.

The original purpose of providing these dates has passed into irrelevance: it was to clarify whether the study was to be done prior to the implementation of GLP regulations.

#### **15.5.12 Test Method(s) (2.-(1) (d))**

If the test method follows or is intended to meet the requirements of a published national or international standard, the appropriate reference should be given. International examples include the OECD Guidelines for the Testing of Chemicals and the EU series of methods specified in Commission Directives. If slight variations from these publications are appropriate, the method could claim to be based on, rather than to follow, the published standard.

#### **15.5.13 Justification for Test System (2.-(1) (e) (i))**

The original reason for including this item in GLP was to ensure that studies were not performed in test systems that were insensitive to the potential hazard under investigation. Latterly, the most common justification for use of the test system is that it is the system required by the OECD or other Test Guideline. However, bespoke studies are occasionally required to investigate specific issues and it is then necessary to show that the test system has been selected carefully, to ensure that manifestation of the potential hazard under investigation is optimised.

In animal and *ex vivo* studies, justification should extend where necessary beyond species, to strain, sex, age or origin of cells or tissues. Field studies may require justification of soil type, crop cover, growth stage and climate. In studies in which the test system is a standard item of equipment, a justification other than the demands of the Test Guideline may be difficult to construct.

For a standard method, careful thought will be needed if it is intended to justify the use of a test system other than that recommended in published guidelines.

#### **15.5.14 Characterisation of Test System (2.-(1) (e) (ii))**

The plan should provide a mechanism for establishing that the test system is as required. A formal process may not be required if the test system is a standard piece of equipment used to determine a physicochemical property; or if the test system has been purchased and delivered against a specification. However, test systems such as soils, cell lines, isolated tissues and bacterial strains may be inadequate in relatively subtle ways, so it may be critically important to investigate and confirm their nature before the study is begun. A microbiological system that has mutated to a less sensitive form, or become moribund or contaminated with wild types, may not be as overtly obvious as (say) an incorrect or inadequate mammalian species.

#### **15.5.15 Method of Administration (2.-(1) (e) (iii))**

The method of administering the test item to the test system should be stated, and again this requirement was included to help ensure that the route of administration would not prevent manifestation of effect. Originally, GLPs were written around mammalian toxicity studies and the issue amounted to the route of dosing – oral by gavage or dietary admixture; by inhalation; or by a specified route by topical application or injection. With the application of GLP to a wider range of study types, the need to specify the method of administration extends to other technologies. For farm-scale field studies, it will usually be necessary to specify hand-held or tractor-drawn equipment; surface application or injection into surface soil; and spray or granule delivery apparatus. In the case of liquid spray, nozzle type may be important in limiting spray drift or ensuring proper coverage of foliage. Conversely, for physicochemical tests involving a test rig, the presentation of the test item is generally an integral part of the test procedure.

In addition, if the test item is presented to the test system in a carrier, it may be necessary to define the concentration of test item and identify the carrier. For dietary admixture studies the carrier will generally be the normal ration; but this should always be stated overtly to avoid any possibility of misunderstanding. Field-study concentrates are invariably diluted to spray-strength with water; nevertheless any requirement to avoid any specific supply (mains, river, rainwater) should be stated. For laboratory studies, the potential choice of liquid carrier is much wider and should be carefully specified. In some cases, it may be more appropriate to specify carriers or solvents that should be avoided. Dissolution or suspension, oxygenation or degassing, pH control and avoidance of contact with specific materials.

#### **15.5.16 Schedule of Exposure (2.-(1) (e) (iv))**

The effects observed during a study will be significantly affected by the extent of contact between the test system and the test item. Therefore, the concentration of test item used, the dose-level per unit bodyweight, or area of application must be addressed. Any untreated or blank-treated controls should also be documented, with clear specification of any blank treatment.

Similarly, the duration of the exposure period (which may range from a few minutes to several years), and the frequency of exposure (one occasion only, daily, annual: pulse or continuous) should be defined as necessary to achieve the study objectives.

Consideration should be given to the incorporation of acceptable tolerances into the exposure schedule. Definition of such tolerances is a matter of scientific judgement, but advance documentation of limits of acceptability may assist with assuring the integrity of the study as well as providing technical staff with clear indications of leeway. However, care should be taken not to quote unnecessarily tight limits that are likely to be exceeded: the widest range that is scientifically acceptable should be used. One threshold value may be sufficient, or a range of several weeks in the case of an annual event.

### 15.5.17 Experimental Design (2.-(1) (e) (v))

This section of the study plan describes the scale of the study, measures to assure its validity, the sequence of procedures and processing of the results. This section is a prime candidate for documentation in an internal company reference document, and might form the “General Study Plan” as described in OECD Principles.

The number and size of replicates, groups or iterations define the scale of the study. In biological studies it is not uncommon for a study to consist of a control and three or four dosed groups on a range of dose levels, each group consisting of a fixed number of animals of both sexes. Physico-chemical studies may consist of a fixed number of iterations of the test process (*e.g.* six trials using the Fall Hammer test for explosivity). Field studies may involve a replicate design of sampling points within the test plot.

The sensitivity, or power of a study is largely defined by its scale. The greater the tested population, the greater the likelihood of detecting a slight effect of the test item; and the more reliable the final result. However increased scale brings increased cost and, in the case of animal studies, increasing concerns for animal welfare. The scale of any study is therefore a balanced compromise between power, resource and ethics: GLP does not address these issues but does require that the outcome in terms of the study scale be documented in the study plan.

Measures intended to control bias in the study, or to verify its validity should be described. Many study plans include a process of randomisation of the test system to ensure that possibly susceptible individuals are not concentrated in one study group: such systems are often not random but are carefully structured to distribute individual properties evenly throughout all groups. The physical arrangement of the study may introduce bias unless care is taken to avoid it: plants near the glasshouse wall, for example, may receive more light and extremes of temperature compared to those nearer the centre. Latin-square designs are often used to preclude such bias. Some short-term studies do not require formal bias control and the test system may be drawn, literally randomly, from a homogenous stock.

Some study designs incorporate tests to demonstrate that the study is adequately sensitive to the effect under investigation. These may consist of additional test groups dosed with a known positive agent, in which failure of the known agent to elicit a response invalidates the study; or some other measure to indicate proper performance.

The necessity for, and selection of procedures required to control bias and assure validity are scientific issues, but every procedure determined to be a necessary part of the study should be described in the study plan.

The technical procedures that constitute the study, and the environment in which the study is to be maintained must be stated. These requirements may be met by a text description of each step of the study, extending to several tens of pages, or may be adequately covered by a reference to a published guideline. Items such as the sterility or grade of reagents; temperature; relative humidity; rainfall; lighting spectrum, intensity and cycle; background counts; pH; oxygen saturation; nutrition or its withdrawal may all be germane to the integrity of the study and if so, should be specified.

Company SOPs may be referenced in the study plan as a convenient shorthand, avoiding the repetition of pages of standard text. However, the danger of referencing specific versions of several SOPs, which may be superseded before or during the study, should be recognised.

It is important for authors of study plans to appreciate that the procedures embodied in the plan define and delimit the study: therefore, activities that are not properly part of the study (pre-study determination of test item solubility or pH, analytical method development, shaving, anaesthesia, test rig cleaning, media preparation, excision of tissue for use as test system, facility quality controls) may not be appropriate for inclusion in the plan. All of these procedures may be done, but some may relate to more than one study (solubility, analytical method). Therefore,



to avoid cross-referencing data between studies or implying that the procedure was done separately for each study, they should be regarded as part of the background facility processes. Other procedures such as cleaning are necessary preliminaries but are not part of the investigation nor shared between studies. They are best described in SOPs. Yet others are clearly part of the study and must be embodied in the study plan (field-scale preparation of test item; collection of pre-treatment data, formation of test item into a specific shape for flammability testing).

The frequency of, or occasions on which each procedure, including measurements, observations and other assessments of response are carried out, should be specified in the study plan. In part, this assures generation of the most scientifically relevant data, but also precludes the possibility of inappropriately enhancing or swamping an effect by focussing observations at particular stages of the study.

### **15.5.18 Statistical Methods (2.-(1) (e) (v))**

The requirement to pre-state the statistical procedures, in advance of any results, can be difficult to meet. While many short-term, relatively fixed-format studies may include standard procedures for data processing, it is often the case that large, complex sets of data require scrutiny by professional statisticians before the most suitable approach may be determined. However, this opens the possibility of selecting a statistical routine that minimises the significance of an unwanted effect. The principle behind this requirement of the study plan is sound: select the process before the choice could be affected by its perceived influence on the outcome.

Where the methods are fixed or known, they should be stated. Where it is not possible or desirable to fully define all the procedures to be used, the study plan should state that the methods to be used are dependent on the nature of the data, and that the methods eventually used and the justification for them will be recorded in the study data.

Chapter 32 provides more information on statistics.

### **15.5.19 Records (2.-(1) (f))**

Good laboratory practices require that the study plan contains a list of the records to be maintained during the study, and many establishments provide such a detailed list in the study plan. The intention is clear: to provide a mechanism for assuring that the necessary records are generated, and a datum against which records can be logged into archival storage (Chapter 36). Most lists, however, include a catchall category to include any items overlooked or unforeseen when compiling the list. This is essential to avoid the inference that an unlisted item need not be generated or retained – the opposite of the intent of the regulation. However, since all study records would fall into this category in the absence of the rest of the list, the practical value of the list may be queried. Other sections of GLP define raw data as “all records and documentation of observations and activities”,<sup>4</sup> and require that raw data and other items should be retained,<sup>5</sup> so it could be argued that a list in the study plan is superfluous.

All the elements of the study plan described so far are mandated by GLP. As a matter of principle, all should be addressed in each plan, even if only to state that the item is not relevant to the particular study type, or that the information is not currently available but will be added by Study Plan Amendment or be documented in the study data. This latter approach may also be appropriate where study procedures are determined by the immediately preceding results. In such a situation, the study plan may describe several options, followed by a statement that the option to be taken will be documented at the time. Since the procedure described in the plan is being followed, no Amendment will be necessary.



## 15.6 ADDITIONAL CONTENT OF THE STUDY PLAN

In addition to the mandatory items listed above, many study plans contain other items, not all of which are necessarily recommended.

All study plans for GLP studies should overtly state that compliance with GLP is required. If necessary, the plan could further identify particular standards, although there should be no necessity to extend this beyond OECD Principles and the national standard of the test institute.

It is usually appropriate to include a section on retention of study raw data. This should state the location of the archive (generally either that of the test facility or the study sponsor), and may usefully include the period of retention and the policy to be observed thereafter. It should not be necessary to list the categories of items to be retained, since this pre-exists in GLP Regulations. However, a clear definition of responsibility for retention of specified data is important in multi-site studies, when the potential for loss through confusion between test sites may be high.

Some study plans, especially for studies performed under contract, include administrative issues such as financial arrangements, the provision of a draft report for sponsor review, number of copies of the final report, or document formatting to meet the expectations of a specific regulatory authority. Unless there is a clear need for such items to be included, they should be reserved for contractual documents. As already explained, the inclusion of such items makes them part of the study and failure to comply (say by providing an incorrect number of copies of the report) constitutes non-compliance with GLP.

In some cases, companies include a process for amendment to the plan, a mechanism for QA monitoring, or other procedures that automatically form part of the study context by virtue of compliance with GLP. Such items are superfluous for a test institute familiar with the necessary standards. Therefore, spelling out basic GLP systems in every study plan could be taken to imply that the facility does not normally operate to, or understand, the requirements.

In summary: the study plan should address all the items specified in GLP plus any additional features considered to be important to ensure the proper execution of the study; but beyond these necessities, the plan should not be confused, obscured or complicated by non-essential detail.

## 15.7 AMENDMENTS AND DEVIATIONS

An Amendment changes the study plan for the future: a Deviation declares that the plan was not followed in the past. Apart from timing, the only difference between Amendments and Deviations is in their distribution and the inclusion of either a justification or an impact assessment. Both documents require the authorisation of the Study Director. Example formats are shown in Figure 2, in which the similarity is emphasised.

Amendments may be required to the future running of the study in the light of early results, as in Figure 2. In other cases the original plan may contain errors: the plan must be amended since GLP requires that the plan be followed, right or wrong! Note that it is illogical (and somewhat fraudulent?) to change the Plan to bring it into line with what was done, so Amendments must not be retrospective. It follows that no amendment can be written once all the planned procedures are completed.

It is essential that all amendments are sequentially numbered and are copied to all holders of the plan. In this way, the study director may be confident that all parties to the study have been fully notified of the study requirements at every stage. Each plan holder should attach his copy of every amendment to his copy of the original plan.

Deviations are failures to follow the plan, but do not necessarily indicate failure to plan ahead. A deviation from plan may arise if an alternative procedure is required because of instrument failure during processing. Alternatively, it may be decided to terminate a study early and immediately for animal-welfare considerations. There may be no time to issue a written Amendment

<p>STUDY NUMBER 2002/23456</p> <p>&lt;TEST ITEM&gt;: REVERSE MUTATION ASSAY USING <i>SALMONELLA TYPHIMURIUM</i></p> <p>STUDY PLAN AMENDMENT No. 2</p> <p><b>Detail of Amendment:</b> the fourth sentence of section 4.4 of the Study Plan (Experiment 2) is amended to require triplicate plating.</p> <p><b>Justification:</b> results from duplicate plates in Experiment 1 yielded variable counts.</p> <p>Authorised by ..... (Study Director) ..... (Date)</p> <p>Distribution: All holders of controlled copies of the Study Plan.</p>
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<p>STUDY NUMBER 2002/34567</p> <p>&lt;TEST ITEM&gt;: DETERMINATION OF EXPLOSIVE PROPERTIES</p> <p>DEVIATION FROM STUDY PLAN No. 2</p> <p><b>Detail of Deviation:</b> the fall-hammer test (explosive properties upon impact) was replicated seven times instead of the planned six.</p> <p><b>Assessment:</b> all seven tests were negative. The result is not affected by the additional determination.</p> <p>Authorised by ..... (Study Director) ..... (Date)</p> <p>Distribution: Study File</p>
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**Figure 2** Examples of a study plan amendment and a study plan deviation

(say, if it was decided this morning to terminate the study this afternoon). Even though the change was planned, the new conditions may be in effect before any paperwork can be raised, so the documentation is retrospective and a Deviation is appropriate. In the above situation, it would be appropriate to include an explanation as to why an Amendment was not produced.

In the case of the equipment failure above, it may be decided to abandon use of the planned equipment altogether, and use an alternative at all future occasions. This would require a deviation to cover the initial crisis and an Amendment to set the alternative future course – although it may be possible to combine both into a single document.

It should be recognised that deviations may arise through the performance of work additional to the plan, as well as work that does not fulfil the plan. But in the example in Figure 2, there would have been no deviation if the number of replicate tests had not been specified originally. This emphasises the earlier point about avoiding unnecessary items or detail in the Plan.

Occasions will arise when a change is required promptly, but the Study Director is not available to authorise the Amendment. GLP does not permit shared responsibility for study direction, yet insists that the plan is followed. The letter of GLP regulations may be met by postponing the

change until the Study Director is available, but this may compromise the study and this is surely not the intent of the regulations. If the change cannot wait, it should be implemented by management and on his/her return, the study director should be advised of events, assess them, document them as a deviation and if necessary produce an amendment for future action.

## 15.8 QUALITY ASSURANCE AUDIT OF STUDY PLANS

Good laboratory practice requires the quality assurance to verify that study plans contain the information required for compliance, and that the verification be documented. In this respect therefore, the stated requirements of GLP are met relatively simply. Figure 3 presents a checklist form that, on completion, would fulfil the requirement. Note that retention of the completed form would constitute documentation of QA verification.

Interestingly, no requirement is found in GLP for the results of QA verification of study plans to be communicated to the study director or management – there is therefore no requirement for acknowledgement or response. Nor is the timing of QA verification specified: so it can be completed at any time between production of the study plan and archiving of the study data. The verification is not an “inspection” as defined in GLP<sup>6</sup> and, as such does not require listing on the Statement of Quality Assurance.<sup>7</sup>

In practice, however, many QA units perform the verification either just before or just after signature by the Study Director, before the experimental start date. This timing allows opportunity

<COMPANY NAME>

**QUALITY ASSURANCE UNIT**

**STUDY PLAN REVIEW FOR COMPLIANCE WITH OECD GLP (ENV/MC/CHEM(98)17) Section 8.2**

Reviewer:	Document:	Date:
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	YES	NO	N/A
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Descriptive Title Nature & Purpose of Study Reference to Test Guideline etc. to be used Identification of Test Item Dated approval by SD prior to Study			
Method of Administration and Justification Positive or Negative Controls to be used Name and Address of Sponsor Name and Address of Test facility Name and Address of any subcontractor			
Location of any remote test sites Name and Location of SD Name and Location of any PIs Areas of Responsibility of any PIs Proposed Experimental Start Date			
Proposed Experimental Completion Date Pertinent Characterisation of the Test System Justification for Choice of Test System Dose levels/concentrations Frequency and Duration of administration			
Detail of design- Procedure, measurements, observations etc Detail of design- Methods & Materials Detail of design- Conditions Detail of design- Statistical methods if used Records to be retained			

**Figure 3** Example of a study plan review document addressing the basic elements of GLP compliance

to correct any oversights, even if by Amendment, in a credible time-scale. In many laboratories, study plan reviews also extend to other issues, the outcome is reported to the Study Director, and a written response is required. In some cases, the verification occasion may be logged within a QA data system and recalled as an item to be listed in the Final Report Statement by Quality Assurance. Whatever the scope of the review and the procedure for handling the outcome, each company should ensure that the system is described in SOPs.

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5. *ibid*, Schedule 1, Part X, 1.-(1) (a).
6. *ibid*, Schedule 1, Part II, 2. (c).
7. *ibid*, Schedule 1, Part II, 2. (f).



## CHAPTER 16

# Standard Operating Procedures for Good Laboratory Practice Work

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## 16.1 INTRODUCTION

An important aspect of a quality system is to work according to unambiguous standard operating procedures (SOPs). In fact, the whole routine work process should be described by a series of SOPs. Writing SOPs for any process an individual or group performs includes the following: identification of specimens, dosing animals, repairing an instrument, harvesting cells, archiving documents and hundreds of other workplace activities.

There will always be employees querying about the meaning of such instructions, and of course you can always question the necessity of it, if it will be used only once in a lifetime.

An SOP can be defined as follows:

*“A Standard Operating Procedure is a document which describes how to perform tests or activities of the investigation. The purpose of a SOP is to carry out the operations correctly and always in the same manner.”*

### 16.1.1 Purpose of the Standard Operating Procedures

The purpose of non-clinical safety studies of test items is to investigate the safety of the test item before use in the clinic. What we should consider is that the SOP is not written for regulatory authorities, but for the company or institution employees. Doing an analysis in the same way every time, no matter who is doing the job, is one of the cornerstones for quality in the laboratory. Therefore, SOPs have to be available at the work place where the operation is performed.

All procedures in the study need to be described and understood by all persons involved. It is not only practical work in studies that needs to be in place, but it is also important to describe the administrative routines that support the activities in a study. It is also necessary that the study be documented in such a way that the testing can be reconstructed years after its completion. Persons not involved in the study may need to do this on some occasions. Such occasions are when colleagues, regulatory authorities or quality assurance (QA) are reviewing the work performed. Using oral communication to instruct and maintain procedures will always result in solutions of individual problems and drift in procedures.

### 16.1.2 The Hierarchy of the Document Pyramid

The top level of the pyramid is the regulatory requirements. This work is defined by specialists from member groups or country delegates (like the OECD). These regulations are harmonised and shall reflect international issues and mutual concerns. A company's QA cannot argue and interpret these regulations as he or she wishes. We have to work with them, and we have to keep in mind that authorities represent the customer/patient, *i.e.* the end user of our product.

Company policies are the second level in the pyramid, and it is the management that describes the meaning of the policy. The third level in the pyramid could be company standards or guides for the employees. The rules in this level are more focused on what to do with the regulations to comply.

The fourth level in the pyramid is the SOPs. It is now up to the users to describe how the work has to be performed. The instruction must be written in the way the work is to be done. Nobody else other than the user can describe this process more accurately. The advice is therefore to make the description clear and simple in a language that is understood. It must, however, be approved by the management.

### 16.1.3 When to Write Standard Operating Procedures

When new equipments or processes create new work situations, there is of course a need for a new SOP. Investigations after your own failure might show you that your own guidelines are insufficient, incomplete or even missing for certain jobs or parts of jobs. Write or rewrite SOPs when new information suggests benefits from modifying work behaviors to improve the procedure.

Systematically update all SOPs by asking workers to evaluate existing ones. If there is a conflict of which should be revised first, then rank these jobs. If some analysis has to be performed within a special campaign work, and there is very little risk that the job is going to be repeated again, then there is a possibility of describing the planned process directly in the study plan and documenting it in the study file.

### 16.1.4 How to Start?

Before introducing SOPs in the organisation and developing their full potential, there is a need to have a quality system implemented in the organisation. The quality policy is the starting point.

It is of utmost importance to have the top management supporting the development and planning phase for the quality system. Those responsible for resources must be involved. Therefore, quality must cascade like a waterfall through an organisation from top to bottom and not the opposite way.

Before writing SOPs of different processes, there must be a document describing what the SOPs will look like. The SOP for the SOPs is most effective if it is a steering template for all procedures. It is relatively easy to decide on what paragraphs should be included and what style shall be adopted for the templates.

Logotype

#### STANDARD OPERATING PROCEDURE (SOP)

Title SOP Format	Work Process Manage Documentation		System GQMS	Scope Global
Replaces A0001, version 2	Effective 2005-02-01	SOP No A0001	Version 3	Page 1 (3)
Written By My Name	Signature <i>My Name</i>			Date 2005-01-15
Approved By Another Name	Signature <i>Another Name</i>			Date 2005-01-20
Cancellation				



Paragraph suggestions are as follows: (1) purpose of the SOP; (2) definitions that must be explained; (3) roles and responsibilities; (4) what do units or departments apply the SOP for; (5) description of the procedure; (6) change log; (7) any references; and finally (8) a list of all appendices.

It is also practical to add the company logotype to all pages that associates to the company and to the end users of the SOP it is produced for. There are other types of information that have to be included and which gives the reader information that is critical. These are as follows: title; SOP number; version of SOP; replacement; effective date; number of pages (incl. pagination); appendices; local/global SOP; author/signature/date; and finally approved by/signature/date. Subsequent pages must contain the SOP identity, number and version, and page number.

It is sometimes convenient to keep information in appendices. These must carry SOP identity page numbering. If the appendices are electronic (e-Appendix) and the company has not implemented the electronic record/electronic signature (ER/ES) legislation, it may cause some problems, especially when technicians are not fully trained in these problems, and do not know what is required from the user. It may be better to print the appendix if there is a user checklist to follow. By converting it back through scanning, the used checklist, with all its information and signatures, is once again an ER. The ER is now a raw data with audit trail and security functions. Both the paper as well as the scanned e-document is considered as raw data in this case (read more about electronic SOPs (e-SOPs)).

### 16.1.5 How to Develop?

It is important to distinguish between prescriptive documentation and descriptive documentation. The trained user normally describes what is to be done, but sometimes forgets to describe existing conditions and mention what can actually happen.

The SOPs should include limitations of each procedure and a list of precautions. For example, the potential presence of natural inhibitory substances should be noted and methods for diluting out or neutralising these substances must be included. The SOPs may also include the roles of personnel to be contacted if out-of-control procedures are found.

The SOPs should also indicate how a test should be read and what should be looked for in a positive and negative test. Colour photographs can be used to assist personnel in reading tests, but it should be kept in mind that care should be taken to ensure that the photographs do not fade. The SOPs can be constructed from manufacturer's brochures and manuals; however, neither should be used as substitutes for SOPs.

Some organisations prefer to use "technical writers" for creating SOPs for others. If resources are lacking, this is a good way of cutting the edge. There is sometimes a cost/benefit argument for doing this. It is however not always the case that the "hired writer" has the technical knowledge of the processes, which can lead to the reaction that the end users do not follow the instructions. Therefore, it is important that the end users can review the draft SOP before finalisation.

### 16.1.6 Regulations and Guidelines

No matter where a non-clinical study is to be performed, in either Europe or the United States, there are regulations that control how to test and assess chemicals/drugs and determine their potential hazards on human health or in the environment.

In the United States, the Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA) officially approve the regulations and guidelines for the US market, while in Europe (EU) all national legislations are historical, and there is just one intergovernmental party "The Organisation for Economic Co-operation and Development (OECD)", representing 30 member states that coordinate and harmonise policies and guidelines. It is interesting that most

countries, including United States and Japan, have all agreed on the OECD Principals of GLP, but some are still using their own regulations.

Independent of official authorities, the most well-known standard for quality is the ISO 9000 family. The documentation requirements within the ISO standard refer to “documented procedures” instead of using the expression SOP. The international standard requires that procedures be established, documented, implemented and maintained, which is in lieu of the SOPs within the pharmaceutical industry.

## **16.2 PRODUCTION OF STANDARD OPERATING PROCEDURES**

As has been said before, the SOP system has to be organised in such a way that it is easy to maintain and keep track of version control and the current list of users. To have someone appointed for the “SOP-life-cycle process” is essential. You will find problems when handling writing-reviewing-updating-maintaining-distributing and archiving SOPs with your left hand and have other roles for your right hand. This is a problem for smaller organisations, where especially secretaries have to combine roles as archivists and SOP administrators besides the role as secretary.

### **16.2.1 Global and Local Standard Operating Procedures**

If a company or institution has a policy with a quality statement and has created corporate standards in a number of fields, describing the purpose and scope of the quality procedure, it is up to the relevant staff to make the rest.

If a company has R&D functions globally, there is a need to create these instructions in the local language. The experience we have and that has been fruitful, is to have global common SOPs written in English, and local SOPs written in another local language. The reason why a SOP is global is because it supports a global service or technique. The local SOPs are considered as local because of the following reasons: (1) less than worldwide use (one or more countries); (2) unique to one local organisational unit; (3) organisational or legal requirements differ globally; and (4) no global need has been defined.

The local quality organisation must be responsible for the administration of the local SOPs. Sometimes there is a favour for a special technique in Europe compared to the United States, and therefore these interests have to be taken into account.

If the SOPs are electronically available on the intranet, it is even better, and they are moreover visualised for the whole organisation. By using e-SOPs it is very easy for global readers to realise that a new release is coming and that previous versions are obsolete.

### **16.2.2 Electronically Available Standard Operating Procedures**

It is more common today that SOPs are distributed worldwide on the company’s intranet. The problem is to decide which is the original copy. Is the paper printout with handwritten signatures the original, or is the Word document or the Adobe Portable Document Format (pdf) file on intranet the original one?

There are different ways to handle these issues. One way is to decide that you consider the paper copy as the original (with handwritten signatures), and that the pdf file (e-SOP) is the copy. Not to mislead the authorities, there is a need for a description in the header saying that a printout is only valid for a defined period from the printing date, and that the printout is an uncontrolled copy. This is something that should be more precisely described for each organisation in the SOP that describes the SOP format.

### 16.2.3 Templates

Some employees are trained in writing and can create an instruction more easily than others. In some organisations, guidance is provided on how to develop and write an instruction. In order to have them more “streamlined”, tools and templates are available on the intranet. Where to find these tools is of course a part of the SOP training.

The template describes the table of content and also gives a brief description under each heading, the meaning and underlying background, which should be considered as relevant information.

For example,

#### *Roles*

[List the major roles for your functional area. Keep in mind that one person can often perform multiple roles. If possible, specify basic training requirements for each role.]

### 16.2.4 Responsibilities

The management group is responsible for the SOP system and the existence of SOPs for the whole organisation. This group has to delegate most activities as they are responsible for the resources, but they do not normally take part in the day-to-day activities in the laboratory. An SOP has therefore to be written by the end user of an instrument or a process. It could be better to define who is the most frequent user of a system or an instrument by having clear roles and responsibilities within the organisation. From our own organisations we have a practice known as the “system owner” concept, which means that this person takes the full responsibility of, *e.g.* an instrument. If the system owner is the only user, somebody from the line management must approve the SOP.

As the text says in the GLP legislation ENV/MC/CHEM(98)17, “... the facility management’s responsibilities is to *ensure that appropriate and technically valid SOPs are established and followed, and approve all original and revised SOPs*”. Normally this is done by management delegation, but this is very seldom done in writing. This can form a practical reason to be described in the SOP for SOPs.

The study director (SD) is designated by the management, and he/she has to *ensure that study plans and amendments and SOPs are available to the study personnel*. The responsibility of the personnel is to *comply with instructions given in the written instructions. Any deviations from these instructions should be documented and communicated directly to the SD*. The QA unit’s responsibility is to *maintain copies of approved study plans and SOPs in use in the test facility*. They are as well designated by the management to assure that GLP principles are followed.

If the organisation is global it might be time consuming to keep track of instruments that can be used in areas other than for GLP. The efforts spent on re-inventing the wheel can be devoted to improve intranet databases for keeping track of “who-has-this-type-of-instrument-somewhere-else”. Benchmarking and best practices may also help the organisation to standardise the processes and improve quality. If there is a need for corporate SOPs or standards, it is very important to have the top management involved in the process. Sometimes the implementation process could even go faster if there is a sign off and approval by top management from other departments, *e.g.* Infrastructure Technology (IT), R&D and Operations, regarding procedures that are common for all disciplines (like how to validate computer systems).

### 16.2.5 Who Has to Sign Off?

All SOPs have to be authorised in order to demonstrate that management has approved that they be released for use. In a previous paragraph it was exemplified what a header could look like. We are aware that policies differ among companies regarding who should sign off and when. We all agree that the author and someone from the line management have to sign off, before it is released.

It is not the president of the company or institution who has to sign off; it is more practical and convenient if this is delegated to someone who speaks with the “doers” on a day-to-day basis. A person who is the manager for the technical staff in the area where the SOP is valid (*e.g.* head of a toxicology unit or head of laboratory) is sufficient. This is of course dependent on the size of the organisation. The effect of this authorisation might come from an individual with organisational influence and specialist insight.

### 16.2.6 Training

Today, there are no problems finding different software solutions that show that end users have read the e-SOP. It is important to keep the records of the training to show that all personnel using a SOP have also got the relevant training. This should be stored in such a way that it is easy to find and retrieve them. By using paper originals, there is a possibility to attach a signature list, which proves that all end users have read and are trained in the current SOP.

A third possibility is to train all users in a department at the same time. What we have to keep in mind is the compliance with ER/ES legislations when we are moving forward in the direction using electronic applications. There is more than one solution to identify that employees have opened the e-SOP. Official SOP training seminars is one way of training.

### 16.2.7 Distribution and Tracking

It is essential to set up a good filing system for all documents right at the outset. This will spare much inconvenience, confusion and embarrassment, not only in internal use but also with respect to the company's management, authorities and clients, and even an accreditation body.

The administrator's responsibility for distributing and archiving SOPs may differ from one company or institute to another. There is a multitude of valid approaches for distribution of SOPs, but there must always be a mechanism for informing potential users that a new SOP has been written or that an existing SOP has been revised or withdrawn.

If the SOPs are electronically available on the intranet, they are even better visualised for the whole organisation. If the SOP is paper based, one of the attachments could be the distribution list for those who need and might use the SOP.

One day, the SOP must be withdrawn and copies of older versions must be discarded and be replaced with the current version. The originals must be archived and the historic originals kept separate from the originals that are valid.

The most logical system seems to make an appropriate grouping into categories and a master index for easy retrieval. It is most convenient to keep these files at a central place such as the office of the administrator. Naturally, this does not apply to working documents that are obviously used at the work place in the laboratory, *e.g.* instrument logbooks, operation instruction manuals and laboratory notebooks.

*16.2.7.1 Archiving Standard Operating Procedures.* One day, new equipment or a new method must be incorporated into the process. A revision must take place. The process or instrument owner has on his agenda to create a new version.

As long as nothing is approved, the old SOP is still in use. The draft is circulating among users and line management. Approval of the new version makes the former version historical. The signed SOP is considered as original, although e-SOPs are used for distribution, which means that the original should be stored and archived. All other copies must be sent to the administrator, who has to destroy all copies. It is not so complicated to archive electronic documents, but to maintain a historic file of SOPs, on a media you can trust for long time, is more complicated.

### 16.3 USE OF STANDARD OPERATING PROCEDURES

The cornerstone for producing high-quality products, services or work is to follow written instructions. Compliance with company SOPs should mirror compliance with current regulations and guidelines as long as the interpretations are based upon understanding the objectives of the regulations. Before employees follow company SOPs, they have to learn and accept them and feel familiar with the concept. Before they can accept them, there must be time for training.

As is stated in OECD legislation ENV/MC/CHEM (98) 17, “... *deviations from SOPs related to the study should be documented and should be acknowledged by the Study Director and the Principal Investigator*”, as applicable.

#### 16.3.1 Deviations

Deviations to written procedures are something that should be avoided, even though it is sometimes not achievable. To develop an alternative process during a study, if something has already gone wrong, is hazardous. To be prepared and identify conflicts, and have the process authorised and judged by QA is more practical. The planned process will achieve better quality as the validity and reliability has been tested prior to the study.

Therefore, it is very important to have the technical staff's understanding of how to proceed when a serious deviation occurs one day. One of the cornerstones is to document promptly what has happened, and remember that this is raw data, and to discuss the impact of the deviation with the SD or the principal investigator (PI).

It is better to have the technical staff involved in the study working with the SD/PI in a proactive way so that deviations are not driven underground. The issue with a deviation is that it can affect the workload as it impacts other staff and areas. If deviations are found repeatedly, either the process has to be scrutinised, and there might be a need for a revision of SOPs, or the technique has to be modified. This may lead to an alternative process, or a better continuity plan (if something goes wrong) or more training of the staff.

#### 16.3.2 Relevant Content

Leave nothing to chance or local variations. When writing an SOP, the author must be sure that every parameter is specified and nothing is open for own interpretations. However, an SOP must give the user a certain type of flexibility. If every single equipment (pipettes, centrifuge tubes, *etc.*) to be used in the operation is mentioned, a deviation would occur the day when a technician chooses another type of tube that differs from the SOP.

If water is used as a dispersant for the test substance, specify whether it is distilled or deionised water or the grade, which should be used. By validating the method before using it more frequently, all aspects that might go wrong can be solved prior to the study. Does the material conglomerate over time or does the material fail to disperse properly? Watch and see. Is there a need for surfactants or additives to the test substance to have it solved? Does the test substance stick to the glass, *etc.*? Sometimes there might be a need to make a pre-test, following the written procedures, without using the “drug” and to see how the experiment was actually performed.

This may be considered as cost effective, especially if the drug is very expensive to purify and involves many people to analyse it. What is missing and what is not relevant in the instructions will immediately be visualised.

The SOPs describe standard procedures, which have proven to be suitable for the organisation. It is sometimes hard to draw the line between trivial and non-trivial operations. As long as a process is under development, there is an excuse for why the QA has not inspected the procedure. The

meaning with the SOP is to not only standardise a process, but also give enough room for conducting non-clinical-testing without regularly violating the SOP. Too much flexibility can in the end lead to more violations.

Cautions and concerns must always be highlighted if solutions used are harmful and may have possible toxicity effects on the technicians. Write warnings and cautions in a clear sentence form. (e.g. – WARNING, eye hazard! To prevent eye injury from spills or splattering, wear safety goggles and face shield in this area.)

### 16.3.3 Where are Standard Operating Procedures Needed?

The OECD GLP principles describe areas where SOPs should be available: (1) test and reference items; (2) apparatus, materials and reagents; (3) record keeping; (4) reporting; (5) storage and retrieval; (6) test systems (where appropriate); and (7) QA procedures.

The phrase “*but not be limited to*” means that other relevant areas should also have SOPs. The following is a list of examples of areas where SOPs should be considered:

- administrative tasks
- communication
- responsibilities in defined roles (not described in the GLP)
- contracting out work
- work environment.

What aspects should be described in the SOPs? The GLP principles give some indications but others may be relevant too.

### 16.3.4 Test and Reference Items

There should be procedures to document the receipt, identification, labelling, sampling and storage of the items. This will also cover the chain of custody of items to ensure that the responsibility for them has been recognised.

The GLP requires that the production of test items needs to be documented. If produced in-house, SOPs can be useful in establishing procedures to ensure proper documentation. What and how much information is needed to ensure the characterisation?

It is necessary to have all steps documented, but it may be supplied to the authority. Purchased items should be referenced by producer and batch identification. All procedures involved in this process need to be described. The characterisation of the items needs to be done. To what extent and when, has to be known well. Who will be responsible for accepting a certain batch of test item to be used in a specific study? The stability of the test item and formulations thereof must be established. This means that during the dosing period it has to be sufficiently stable. Whether this is done before starting the study or during the routines needs to be described in SOPs. Another routine, which needs to be described, is how the test item is requested for a study. The transportation and the handling needs might as well be documented. Who is responsible for what in this process? All transfer and use of test items must be described to make it possible to see how much was used and if anything remains and what will happen to that?

### 16.3.5 Apparatus

The procedures for use, maintenance, cleaning and calibrations are mentioned in the GLP principles. Other aspects to consider are how to keep a record of these activities and also repairing. Certain instruments may need acceptance testing or validation before taken into use and such



internal requirements can be described in SOPs. If there is a system of persons being responsible for instruments or groups of instruments, the extent of responsibility should be described. If service of instruments is performed by other departments or external organisations that is also to be described. This can be done in SOPs or referred to in logs for the respective instrument.

Special attention is given to computerised systems where the following areas are covered: validation, operation, maintenance, security, change control and back up. It is essential that the validation be followed up with change control to maintain a status of being validated during its lifetime. In case the system is installed in a network, it is important that the performance of the network is controlled and kept updated. The issue of compliance with FDA 21 CFR part 11 for electronic records and electronic signatures is also to be considered.

### **16.3.6 Materials, Reagents and Solutions**

Procedures for preparation of reagents and solutions need to be described. This includes how to label and establish their stability. Purchased reagents or chemicals, which have no set expiry date, need to be given expiry dates or other means need to be used to ensure their suitability. One way is to mark the container with the date it is opened. In this case scientific judgement will be used to evaluate the suitability. Such rules need to be described in SOPs.

### **16.3.7 Record keeping, Reporting, Storage and Retrieval**

The following are considered to be described in SOPs: coding of studies, how data is collected, preparation of reports, indexing systems and handling of data, including the use of computerised systems. The indexing system includes the indexing of SOPs. Definition of raw data is needed in general or for each system generating raw data. Archiving for a secure storage also needs an index system to keep track of what is archived. In the long run, it is important for easy retrieval of materials.

The SOPs are needed to describe how study plans are prepared and reviewed. The indexing system for studies has to be described to ensure that when a study plan is finalised by the SD signature, the identity will remain with the study and that it is recorded in the master schedule for the facility. Also, how to maintain and update the master schedule has to be well described. Procedures need to be described for the creation and handling of study plan amendments and study plan deviations.

A definition of what is a raw data in the study is usually required. If collection is done electronically, it has to be described if the first print out is raw data or if it is still kept electronically. When electronic collection of raw data is used, consideration to FDA's 21 CFR part 11 has to be given.

The SD is responsible for generation of the study report. The procedures for generation, quality control of data produced and transferred into the report, scientific review, QA review and finalisation need to be defined and described in SOPs.

The study is not completed until the study plan, raw data, other documentation, the report, samples and specimens have been archived. The procedure for these activities is a subject for a SOP. It can also contain information on the standard for what shall be archived.

There must be an identified archivist who has to make sure that all material is properly placed in the archive. It must be indexed for easy retrieval. Will loans from the archive be permitted and if so, who will authorise the loan and when must it be returned?

### **16.3.8 Test Systems**

The test system is crucial in the study and the GLP principles are detailed in what is required. It has to be remembered that test systems are not necessarily animals but can also be cell cultures or



preparations thereof and also physico-chemical systems. The definition given in the GLP principles is as follows: “*Test system means any biological, chemical or physical system or combination thereof used in a study*”. Most of the points to consider refer to handling of animals. It must be remembered that appropriate measures have to be taken for other test systems.

The preparation of rooms for the test system and what environmental conditions will be used and how that is monitored and documented has to be described. Also how alarms are acted upon, need to be described. The limit for the environmental conditions are usually set by authorities. If computerised system is used for monitoring, it has to be validated as other such systems. The SOPs for validation need to be in place. The receipt and handling of the test system regarding identification, characterisation as well as transportation and where it will be placed have to be described as well. It has to be observed and examined during its storage before and use in studies. Procedures must be in place to take care of moribund and dead animals in the study. Usually, the study plans give detailed information of what to do with these animals, but there must be a written procedure too, in case this happens before a study.

Randomisation procedures should be described for inclusion in study groups as well for how the animals will be placed in racks. This must also contain information about rearranging the cages during the study in order to minimise environmental conditions to have an effect on the study. Procedures are needed for sampling, *e.g.* blood sampling and preparation of sera or plasma, and for collection of specimens, *e.g.* at necropsy and for histopathology. This should include labelling and handling of samples and specimens.

### 16.3.9 Quality Assurance Procedures

The operations performed by the QA personnel need to be described in SOPs. These will include inspections (facility, process and study specifics) and frequencies of them. Any inspection of contract research organisations (CROs) and suppliers needs also to be identified. How results from inspections shall be reported should be described. Inspections will include reviews of study plans and study reports. The purpose of the different inspections should also be explained.

### 16.3.10 Other Areas

There are other areas where it is appropriate to have SOPs to ensure that work is well organised and easily understood. Administrative routines need their description for creating and maintaining updated documents like organisation charts, job descriptions, curriculum vitae and training records. Illness, sickness and employees' healthy status could also be a risk, as transfer of airborne viruses or throat bacteria are much higher when employees' health status is not accurate. Technicians should inform the SD if their daily work is dosing animals or, *e.g.* harvesting cells, to avoid the study being spoiled because of incorrect results.

All this is needed to be able to identify who is trained for what procedures and to be accepted for performing the tasks. It has to be emphasised that the SOP for SOPs is vital to keep control over the SOP system. The newly defined area multi-site studies (ENV/JM(2002)15) require details about responsibilities and communications. It is important to describe the communication between different functions, SD, PI, responsible scientist and quality assurance units (QAUs) at test facilities and test sites. Roles for the communication with external CROs is advantageous to ensure the communication lines, *e.g.* define the role for the sponsor representative to have the responsibility for communication with a SD at a CRO. It is also described in the GLP that there should be “*clear lines of communication*”. It is the responsibility of the management to establish and describe the hierarchy of who is reporting to whom, and how information shall be treated.

## 16.4 SUMMARY

Work to be performed in non-clinical safety studies is described in study plans. For practical reasons, the routine procedures are described in SOPs instead. This will also ensure that the procedures are performed in the same way in all studies.

The creation, distribution, revision and withdrawal of SOPs are important tasks and require good control. The SOP administrators do have an important role. When defining responsibilities it is advisable to refer to functions rather than to persons. The level of details in SOPs should be sufficient to give a good description that is well understood by those who will use it. If the descriptions are too detailed, deviations will occur frequently and this should be avoided for several reasons. One is the respect for the SOP system. Anyhow, all work should be documented to make it possible to reconstruct the study.

Each organisation has to decide which SOPs are needed, how the material is organised and the level of detail required. Depending on the organisation the practical aspects must be considered; whether SOPs will contain large parts of work or if it is easier to maintain SOPs for smaller areas of work.

## FURTHER READING

1. Principles of Good Laboratory Practice ENV/MC/CHEM(98)17, OECD, Paris, 1998.
2. Good Laboratory Practice: The application of the OECD principles of GLP to the organization and management of multi-site studies ENV/JM(2002)15, Paris, 2002.
3. GLP Consensus Document. The application of the principles of GLP to computerized systems. OECD/GD(95)115, Paris, 1995.
4. Good Laboratory Practice for nonclinical laboratory studies. Federal Register 21 CFR, Part 58.
5. N. Gawadi, in *Good Laboratory and Clinical Practice*, P.A. Carson and N.J. Dent (eds), Heinemann Newnes Publishing Ltd, Oxford, 1990.



# Inspections: Procedural, Process and Facility

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## 17.1 INTRODUCTION

Audit may involve a range of techniques for examination of activities, materials and records. In all cases the aim is to establish whether criteria have been established and have been/are being met.

Audit commonly focuses on *output* to determine that standards have been met. Common types of output audit include: data, record and final report audits under GLP and trial file, source data/case report form and consent records under GCP. While these can provide some information regarding the quality of the work examined, there are limitations.

The first limitation is obvious – if errors are found in outputs the error has already occurred. It may be possible to repair the error but this will involve repeat work. It may also be possible to use the information gained to prevent a recurrence of the error, but the fact remains that the error has occurred. The second limitation is more subtle – the possibility of “false negative” findings. It is feasible that apparently acceptable records may be based on flawed procedures. The correctly signed consent form does not prove, beyond any reasonable doubt, that the subject was given the proper information in the proper manner. The record of animal dosing is not infallible proof that the animals were actually dosed.

Auditing *performance* can reduce the risk of false negative findings. I use the term “reduce” carefully since an audit of performance demonstrates only the potential for the system to operate correctly. It may be reasonable to infer from the audit that the system operates in a particular manner but this is only possible to infer in the absence of continuing actual observation. Performance audits are commonly referred to as “in-life audits” or “*inspections*”.

## 17.2 TYPES OF INSPECTION

The OECD Principles of good laboratory practice state:

*Inspections can be of three types as specified by Quality Assurance Programme Standard Operating Procedures:*

- *Study-based inspections,*
- *Facility-based inspections,*
- *Process-based inspections.*

The revised OECD Consensus Document, “Quality Assurance and GLP”, goes into more detail:

*QA programmes are frequently based upon the following types of inspections:*

- **Study-based inspections:** *These are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study.*
- **Facility-based inspections:** *These are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.).*
- **Process-based inspections:** *Again these are performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature and are generally performed on a random basis. These inspections take place when a process is undertaken very frequently within a laboratory and it is therefore considered inefficient or impractical to undertake study-based inspections. It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases.*

From the above definitions, process-based and study-based inspections have much in common and only differ fundamentally in whether or not a specific study is being targeted. Both these types of inspections operate at the micro level. They are complemented by the facilities inspections, which operates at the macro level to see how the different elements come together.

Some organizations distinguish between facilities audits and systems audits in order to take the meaning of the word “facilities” literally but GLP does not make this distinction.

The inspection process will be described below, initially using facilities inspections as the model. This is because the facilities audit is probably the most demanding in terms of organization, preparation, planning and conduct. Procedure and process inspections have a much more tightly defined scope. The principles of preparation and planning still hold for these inspections but they are generally less complex than facilities inspections.

### 17.3 FACILITIES INSPECTIONS

The facilities inspection is one of the fundamental activities in the assessment of compliance and quality. GCP site inspection/audits are discussed in Chapter 5. It is no coincidence that, in the United Kingdom, the first formal activity that the GLP Monitoring Authority will undertake when a laboratory enters the compliance programme is a facility inspection. Later inspections will concentrate on the effectiveness of compliance implementation in detail, focusing on particular areas, but the initial inspection is used to determine the effectiveness of GLP and is, thus, an overview.

For individual laboratories the purpose of the facilities inspection is the same – to obtain an overview of the competence and quality of a laboratory or company. This is commonly required when a laboratory is to be used as a subcontractor for part or all of a programme of work. A facility inspection should be undertaken to determine the basic acceptability of the laboratory before detailed technical discussions on the programme are initiated. The same applies in-house when a new facility requiring GLP compliance is introduced.

While the need for facilities inspections of new subcontractors or in-house functions is obvious, there is also value in repeat facility audits of existing operations, usually annually or once every 2 years. The reasons for this are:

- (i) To cover areas that may not individually be inspected by study or process inspections.
- (ii) To assess how well the discrete functions, which comprise the operations of the facility, interact.

To elaborate, one potential weakness of the normal approach of QA inspections is that they concentrate on discrete, well-defined units (phases of studies or processes). As such, they can overlook important management operations that do not fall into such discrete categories. Training standards and records are examples of areas that are often not examined on a study or procedural basis, nor are often organization charts, policy documents *etc.*

Equally, while QA audits and inspections may be powerful tools in assessing how well phases and procedures operate, they may overlook one of the most critical aspects of quality – How well these interact with each other? To provide the most effective promotion of quality it is necessary to identify areas of potential error, and prevent errors *before* they occur. Interactions between different areas of a facility represent a particular risk. Any weaknesses in understanding can cause errors. Equally, areas may control materials and information within their own boundaries well, but transfer of such information or materials to other areas can be risky.

Inspection of study phases and procedures may commonly miss these important risk factors. Periodic facility inspections are the most effective method of control.

### 17.3.1 Preparation

As with all inspections, preparation is vitally important. Without proper preparation the facilities inspection will be, at best, inefficient.

Ideally, the preparatory phase should be conducted before arrival at the facility to be inspected, or a separate pre-inspection visit may be undertaken, if this is convenient. Alternatively the preparatory phase may form the first part of the inspection, but this does not allow as much opportunity to reflect on and plan the actual inspection. Whichever method is adopted, the preparation of the inspection is critical – possibly the most critical aspect of the inspection – and must not be overlooked.

The exact nature of the material required to plan an inspection properly will vary, depending on the facility and what background information already exists (for in-house activities or a previously inspected laboratory), but generally it should include:

- (i) *A description of the history of the facility.* This provides valuable background information, particularly on the experience and stability of the facility.
- (ii) *An overview of the facilities and functions.* This can include such information as brochures and floor plans, which will give an indication of the range of activities undertaken and the extent of the operation. In addition to permitting a preliminary assessment of whether the facilities appear adequate, this will give an indication of the amount of time that may be needed for an inspection – there is nothing worse for the inspector than a rushed inspection, or more irritating for those being inspected than an inspection that is padded out.

While many facilities will be only too willing to provide you with brochures, there may be an understandable reluctance to provide more sensitive information, such as floor plans, since these do represent commercially-sensitive material and could cause real harm to the facility if they fell into the wrong hands. Thus, in asking for such items as floor plans, you should give guarantees of security and confidentiality, and if the laboratory refuses, this should not be taken as indicating that there is anything to hide!

- (iii) *Organization charts.* These provide valuable information regarding the operations and reporting responsibilities. Of particular importance is the independence and level of reporting of the quality assurance unit (QAU).
- (iv) *Curricula vitae of senior staff.* An assessment of the experience and competence of the senior scientific and technical staff of the facility is an important part of the facilities inspection. Requests for *curricula vitae* should be selective. There is no need to have this

information for other than key personnel at the planning stage in order to assess if there are enough experienced staff in key positions. Follow-up in more detail may be deferred to the actual inspection.

- (v) *Index of Standard Operating Procedures.* The facility should have an index of standard operating procedures (SOPs), and ideally this should contain at least the title, author and date of the last review or revision. Obtaining this list in advance of the inspection can save time by permitting pre-selection of those SOPs that the inspectors are most likely to wish to examine during the inspection.
- (vi) *Index of types of test.* If this is available, it can help with planning which activities are most relevant to the inspection and should be inspected in detail. It is also useful in assessing if the facilities are likely to be adequate for conduct of such tests.
- (vii) *Sample protocol.* An example of the facility's standard format and content of protocols will permit checking that all the elements required by GLP are addressed.
- (viii) *Sample SOPs.* It is useful to have some examples of the facility's SOPs. While it is important to recognise that there will be stylistic differences, depending on the policies of each facility, there must be clear evidence of the control of the SOPs (authorisation and approval, prevention of unauthorised copying and issue control); and the SOPs should neither be so vague as to be useless for standardization or so detailed that they are unusable by staff. An overly long and detailed SOP may look superior to a terser version, but if it is too long, you can be fairly certain that the staff will avoid referring to it because of its complexity! SOPs should be brief and to the point.

Since you will probably wish to examine the QAU's SOPs in some detail, you may wish to request some of these as examples, with perhaps representative operational SOPs and the SOP on writing and controlling SOPs. Again keep requests to a sensible minimum. The aim is to get a flavour of how the facility addresses SOPs, not to overburden the facility with providing unnecessary material. There will be plenty of opportunity to follow up on more SOPs during the actual inspection, and, more importantly, see them in use.

- (ix) *Sample training records* (Chapter 39). During the inspection you will probably wish to select some training records for detailed examination. However, there are benefits in familiarisation with the format of training records at the planning stage. Blank records to a standard format (or the SOP on maintenance of training records) prevent confidential information being provided.
- (x) *Policy statements.* Where the facility has policy statements (*e.g.* a general policy about the applicability of GLP to its operation; the policy on the appointment of study directors, if this is not covered by an SOP; and the policy on staff training/health), provision of these at the planning stage will give an impression of the environment of the facility as regard GLP compliance.
- (xi) *Details of government inspections.* Where the laboratory is part of a GLP-compliance monitoring programme organised by government, it is important to obtain details of government inspections. With certain authorities, *e.g.* in the United States, full details of the inspection are a matter of public record, and the laboratory should be easily able to provide them. In many other countries, including the United Kingdom and Japan, the details of the inspection are normally confidential between the government inspectors and the laboratory, but a certificate is issued when the inspectors consider the laboratory to be in compliance. It should also be noted that some countries do not operate a programme of routine inspections, and laboratories in these countries cannot provide evidence of periodic inspections. Where a national authority operates a random or "for cause" programme of inspections, whether or not a laboratory has ever been inspected is outside the control of the laboratory.



The use of laboratories, which are not part of a compliance programme, has to be judged on an individual basis. There are circumstances where specialist techniques that form only a small part of a study, *e.g.* specialist chemical analyses, may require to be performed in such a laboratory, and provided that the conduct of the work is carefully monitored and the principles of GLP are applied, there should normally be no problems. There are set procedures for such subcontracting in some countries such as the United Kingdom. If in doubt, consult the relevant monitoring authority for advice.

You should also consider membership of other quality systems such as laboratory accreditation schemes (*e.g.* ISO 17025 and CPA) and ISO 9001, but ensure that the scope of these systems is relevant to the work being performed (see “Glossary”).

This list is by no means comprehensive, but represents the typical core information required for proper planning of an inspection.

In asking for such material, it is important to stress again that selectiveness is important. Asking for too much material is not only burdensome on the facility but may cause you unnecessary extra work without additional value. Many facilities will have a standard dossier, which will cover much of the material required.

Finally, should a laboratory have a policy that prevents provision of some material off-site, it is only courteous to respect this policy – and good sense to ensure that the material is examined on-site.

### 17.3.2 Planning

Having obtained the necessary background information either before the inspection or at the beginning of the inspection, you will find it useful to prepare a plan for the inspection. Many inspectors like to start with a walkabout to familiarize themselves further with the facility. Little detail is required at this stage, since it is an extension of the preparation phase, and is mainly useful in identifying those areas to be examined more closely or apparent gaps in the facilities you would expect to find.

From your preparation, there will be a number of areas you wish to follow up in more detail, for reasons of clarification, special interest, or identification of possible weakness or non-compliance. It is valuable at the start of the inspection to indicate those areas you wish to focus upon, so that the area staff can be available with minimal disruption to both parties.

In addition to those items you select as a result of your preparation, there are certain pivotal areas that should form part of a facility inspection.

### 17.3.3 Opening the Audit

Having completed your preparation and planning you will want to start the inspection. For every significant inspection (certainly for every external inspection) you will start with the *opening meeting*. This is the opportunity to go through your agenda to ensure that the people and resources you need would be available during the inspection. It is also a further chance to fill in any gaps in your knowledge of the facility and its systems. During this meeting you will explain the procedures for the inspection and how (and to whom) outcomes will be reported.

### 17.3.4 Studying the Study Director

One of the central tenets of GLP is the effective action of the study director. During a facility inspection, the experience, effectiveness and commitment of study directors must be assessed.

Clearly, the study director must have sufficient training and experience to perform his duties properly. This can be assessed largely from his curriculum vitae, supplemented with a few minutes' conversation.

During the inspection it is important to assess his involvement and effectiveness. What evidence is there that the study director is in contact with his studies and knows what is happening? Does he have control over amendments to and deviations from the protocol? What happens if he is not available for any reason? Does his staff know his requirements? In short, is he on the ball?

In answering these questions, there is no substitute for inspection. Many of the questions can be answered by discussion with typical study directors, but it is also important to determine if there is any documented evidence that he is a participant in the live conduct of the study. In complex studies, it is unrealistic to expect the study director to be expert in all areas contributing to the study. It is, however, quite realistic to determine how he ensures that the contributing areas meet his requirements, and how he retains control of the study.

In multi-site studies, the study director may be supported by principal investigators in certain defined phases of the study, but the study director retains final responsibility and authority over the study. It is appropriate to examine the methods by which the study director is kept informed of the conduct of the study, especially if there are any problems. Much of this will be defined in study-specific information and should be covered by study-procedure inspections, but it is appropriate to examine the general arrangements if there is a possibility that a multi-site study might be involved.

One of the principal problems often encountered is precisely the duality of the role of the study director. He must be both senior enough to have the experience to design, run and interpret the study properly, and yet have the opportunity to play his part in its conduct. This is best judged by determining the number of studies run by a single study director at any one time.

In order to maintain the necessary contact with the studies and provide a clear line of responsibility during the study director's absence, some laboratories have deputy study directors (sometimes called study supervisors or project leaders). There are potential strengths in such systems, particularly for major studies, but if such a system exists, it is still necessary to determine if there is delegation of duties to the extent that the study director does not meet the requirements of GLP by being too remote from the study.

## **17.4 LOOKING AT QUALITY ASSURANCE**

Quality assurance (QA) is of importance when the facility is not in-house, and it is provided by the facility's own QA function. Clearly, when you are relying on another QA function to provide monitoring of studies, you will wish to be assured that the QA function is acting to acceptable standards.

Examination of the QA SOPs (if provided for the preparation of the inspection) will give a good idea of the philosophy and practice of the QA function. During the inspection you will wish to be assured that (1) the QA function has sufficient, properly trained staff for the conduct of its duties, (2) there is adequate management support to ensure that the findings of the QA function are properly addressed and (3) you will be able to determine what inspections and audits are conducted in relation to work you place in the facility. It is particularly useful if you can have access – in confidence – to the records of the QA function relating to your own studies rather than just a list of dates and phases inspected.

### **17.4.1 Considering Test Substance Control**

If the activities of the facility include the administration of a test substance, it is important to ensure that there are adequate controls over its use. Record-keeping systems should be adequate, so that you can reconstruct the use of all the test substance supplied to the facility. Facilities must be capable of storing the test substance securely, in accordance with the requirements of the protocol. Labelling systems must be adequate to ensure that the test substance is properly identified and used, with no risk of confusion.

Clearly, the integrity of any study depends critically on the correct administration of the test substance. If for any reason this is not properly controlled, then there are great risks to the quality of the study. Hence test substance control is worthy of particular attention during a facilities inspection.

#### 17.4.2 Considering Data Control

Whatever the nature of work in the facility, it will produce data. The facilities inspection should thus concern itself with the quality of data production and retention.

Examples of data-recording systems and standards should be examined, with particular emphasis on what quality control measures are adopted to ensure that the data are accurately recorded and retained. Where data are recorded directly on-line by computer systems, examination of the validation of those computer systems is required.

Accidental loss of data has obvious and serious consequences for the validity of studies. Inspection of the archive is a self-evident and important aspect of facilities inspection, but security of the data at all stages is well worth consideration, since they are probably at greatest risk before formal transfer to the archive.

### 17.5 THE INSPECTION

Given proper preparation and planning, the inspection itself should achieve its intended purposes with ease. Indeed much of it will be spent in confirmation of information gleaned during the preparation and planning stages, either by direct observation or discussion with the staff.

The inspection process calls for the same skills that any QA professional will have used on many occasions, except for two particular challenges:

- (i) *The identification of gaps.* It is relatively easy to assess the adequacy of those items that you see. Since it is the *overall* compliance of the facility that concerns you, it is as important to identify those items that you would expect to be present but did not see.
- (ii) *The breadth of vision.* Again, since this is an overview inspection, it is necessary to pay attention to the interaction of the various functions of the facility. Does the animal room receive adequate support from the feed store and the cleaning facilities? How does information regarding study requirements flow between areas? How does QA know what is happening in the facility? How do the various areas plan their activities so that there are no unjustifiable delays in the conduct of the study?

Thus the facilities inspection requires a greater degree of mental flexibility and lateral thinking than the inspection of a well-defined process or phase of a study. It also calls for a much greater degree of judgement as to what is important or trivial, what is wrong or just different.

The importance of the flexibility of thinking that is critical to a good facility inspection may seem to argue against the use of checklists. However, in the full inspection of, for example a contract toxicology laboratory, there are so many aspects to be covered that a checklist is of value in ensuring that all aspects are examined. An example of such a checklist is attached as an appendix to this chapter.

#### 17.5.1 Debriefing

The debriefing session at the end of such an inspection is important. Not merely is it common courtesy to let those being inspected know of your findings, but it can also help to clear up

misunderstandings before they form part of the inspection report and lead to unnecessarily optimistic or pessimistic conclusions being drawn.

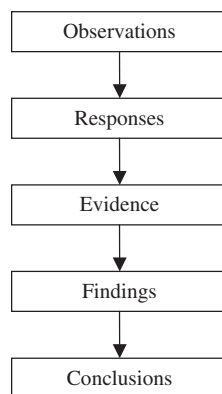
All the key personnel affected by the inspection should be given the opportunity to attend the debriefing, and the opportunity taken to make comments – both positive and negative – on the conduct of the inspection.

While there is a temptation to gloss over any particularly unsatisfactory points, this temptation should be resisted. It is not constructive to leave the facility with the impression that there are no points of great significance, only to send an adverse report later. The written report should contain no surprises, positive or negative.

The debriefing should be approached with a constructive attitude on both sides, even when adverse comments are made. The facility can learn from the experience of the inspector, but equally the inspector can learn from the different approaches adopted by the facility.

After the inspection, a written report should be provided to all parties whose work has been inspected. This has two purposes: (1) to record all items that were inspected, and (2) to indicate the conclusions of the inspector.

While it may be that the inspector may have all the necessary information by the end of the inspection, this is not always the case. The inspector will then produce a list of *observations* to which he requires responses. These observations plus the responses represent the *evidence* against which the inspector can judge if the audit *criteria* have been met. It is only once the evidence has been evaluated that the inspector can make the *audit findings* and draw his *conclusions*.



The record of the inspection is relatively straightforward. It is a list of all the items inspected, perhaps in the form of the checklist used. While this can be tedious, it is important to define exactly what was inspected for future reference in case there is any lack of clear understanding regarding the scope of the inspection.

The conclusions of the inspector should place the major findings of the inspection in context, and recommend possible corrective actions where appropriate. In facilities inspections, more than many other types of QA inspections, one seldom deals with cases of black and white. It is more likely that problems noted will range over a spectrum from the potentially serious to the relatively trivial, and the inspector who merely lists adverse findings without placing these in context does himself no favours. It is much better to highlight those items that deserve rapid and serious attention, while giving lesser prominence to matters that are unlikely to cause serious mishap to studies.

In summary, the reader of the report should be able to obtain a detailed picture of the content of the inspection and form a balanced view of the strengths and weaknesses of the facility. To merely provide a list of problems on the basis that it is up to someone else to make the judgement as to their consequences is to avoid making essential professional judgements.

## **17.6 DIFFERENCES FOR PROCEDURE AND PROCESS INSPECTIONS**

The above principles apply to all types of inspections, but the degree of application may change for procedure and process inspections, especially if they are in-house.

### **17.6.1 Opening Meeting**

The opening meeting should only be as formal as is required to achieve the purposes of the inspection. It is always essential to ensure that auditees are aware that an inspection is taking place and to ensure that the correct procedures or processes are taking place.

The degree of formality is dictated in large part by the familiarity of inspectors with the people and practices being inspected. A short introductory meeting, at which the inspector receives explanations of what is happening, can avoid misunderstandings and unnecessary interruptions later in the inspection. Even this may be unnecessary during routine inspections of in-house procedures.

However, bear in mind that the purpose of the opening meeting is not merely administrative; it ensures that both sides are committed to the audit. An inspector who starts an inspection without contact should not be surprised if he is ignored! Sometimes the purpose of the opening meeting is covered by regular meetings at which inspections are planned with auditees, but at the very least the inspector should always check that he is in the right place at the right time and that it is safe to conduct the audit.

### **17.6.2 Debriefing**

Similarly, a formal exit meeting after routine, in-house inspection is neither necessary nor logical. On the contrary, it is necessary to indicate the end of the inspection and provide any significant comments (or a commitment to discuss these at a convenient time in the very near future).

### **17.6.3 Announced vs. Unannounced**

The majority of inspections are pre-arranged, often some time in advance. This is usually a matter of simple logistics and cannot be avoided.

The purpose of an inspection is to observe facilities, processes and procedures as close to reality as possible. The announced inspection does not achieve this. It only measures potential, not reality.

Having announced an inspection some time in advance the auditees will have used that time to ensure they are in the best possible condition for inspection. Consequently, if there are findings during an announced inspection it tells you that they do not understand the requirements, and incapable of meeting them – or don't care! What it does not tell you is that they continue to behave in this manner when not being inspected.

Completely unannounced inspections are seldom practicable but reducing the time between arranging and carrying out the inspection will bring observations closer to reality.

## **17.7 CONCLUSION**

The facility inspection represents one of the most interesting and challenging parts of a QA inspector's duties. During it he will deal with complex systems that will call upon all his inspectional experience and challenge the flexibility of his thinking. A good facility inspection can be of enormous benefit to all parties, and above all else the facility inspection provides an excellent opportunity to promote the best type of quality – one based on prevention rather than detection of errors.

## APPENDIX: SUGGESTED CHECKLIST FOR FACILITY INSPECTIONS

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1. Organisation and personnel
  - 1.1. Is a current organisation chart available for the facility and each area within the facility?
  - 1.2. Is a current floor plan of the facilities available?
  - 1.3. Is there a policy on training staff, both within the facility and externally?
  - 1.4. Are there records available to indicate the job description and level of competence of staff?
  - 1.5. Is there evidence of regular review and update of these records?
  - 1.6. What arrangements exist to ensure that staff do not adversely affect the conduct of the study through illness?
  - 1.7. Are there adequate numbers of staff available at the appropriate levels for the conduct of studies?
  - 1.8. What mechanisms exist for the appointment and replacement of study directors, and how are these documented?
  - 1.9. Are there methods of planning work loads to prevent overload of study directors and other staff?
  - 1.10. Is there evidence that staff at all levels clearly understand the requirements of the study?
  - 1.11. Is there a procedure for participating in multi-site studies?
  - 1.12. Is there a mechanism for the appointment and replacement of Principal Investigators?
2. Quality Assurance
  - 2.1. Is there a Quality Assurance function?
  - 2.2. Is it independent of the conduct of studies?
  - 2.3. Do QA staff have any other duties?
  - 2.4. To whom does the QA function report?
  - 2.5. Does the QA function receive copies of all protocols, amendments and other relevant material governing the conduct of studies?
  - 2.6. Where is this material kept?
  - 2.7. Does the QA function approve or review all protocols?
  - 2.8. How and by whom are critical phases of studies selected for inspection?
  - 2.9. What is the frequency of study-specific inspections?
  - 2.10. Are study-specific inspections unannounced?
  - 2.11. How and by whom are procedural inspections selected?
  - 2.12. What is the frequency of procedural inspections?
  - 2.13. Does the QA function conduct facility and other inspections of subcontractors?
  - 2.14. What is the frequency of facility inspections?
  - 2.15. What is the mechanism and format of reporting inspection findings?
  - 2.16. Who receives copies of the inspection records?
  - 2.17. Is there a system for follow-up of inspections where corrective actions are advised or required?
  - 2.18. Are records of QA inspections available to sponsors?
  - 2.19. Are records of QA inspections available to government inspectors?
  - 2.20. Does the QA function conduct data audits during the live phases of studies?
  - 2.21. Does the QA function audit interim, draft or final reports?
  - 2.22. What is the mechanism for QA approval of final reports?
  - 2.23. What is the format of the QA statement in the final report?
  - 2.24. What is the mechanism for reporting audit findings?
  - 2.25. What is the mechanism for follow-up on audit findings?



3. Facilities (general)
  - 3.1. Is there a clear definition of responsibility for each area within the facilities?
  - 3.2. Is there a clear requirement for the health, safety and hygiene requirements on entering each area of the facility?
  - 3.3. Are all facilities maintained in a good state of repair and tidiness?
4. Animal facilities
  - 4.1. Are animal facilities of suitable size, location and construction for their intended purposes?
  - 4.2. Is there a separation of 'clean' and 'dirty' areas?
  - 4.3. Are different species housed separately?
  - 4.4. Are studies housed separately?
  - 4.5. Are all animals uniquely identified, where practicable?
  - 4.6. Are all cages uniquely identified?
  - 4.7. Are there full records of the receipt, use and reallocation of animals?
  - 4.8. What quarantine arrangements and health checks on newly received animals are conducted, and how are these recorded?
  - 4.9. Are animals permitted to acclimatize to the facilities before commencement of studies?
  - 4.10. What procedures exist for the identification and isolation or disposal of diseased animals?
  - 4.11. What environmental control standards (e.g. temperature, humidity, light intensity, air changes) are set?
  - 4.12. How are these monitored?
  - 4.13. Do procedures to deal with environmental control failure exist?
  - 4.14. Are records of environmental control maintained?
  - 4.15. Are there written husbandry standards, and are these being followed?
  - 4.16. Are there written records of routine husbandry?
  - 4.17. What are the procedures for cage, rack and other equipment cleaning and sanitization?
  - 4.18. Are there quality control checks on the adequacy of cleaning and sanitization?
  - 4.19. What are the procedures for disposal of waste from animal rooms?
  - 4.20. Are there separate areas for the storage of feed and bedding?
  - 4.21. What control measures are there to prevent contamination of feed and bedding (e.g. by rodents and other pests)?
  - 4.22. Are there records of analyses for feed, bedding and water?
  - 4.23. Are there routine methods of pest control?
  - 4.24. Where pest control calls for the use of chemical agents, are records maintained of their use?
  - 4.25. Do the activities of the facility comply with local legislation and regulations regarding the use of animals for scientific purposes?
5. Test and control substance handling facilities
  - 5.1. Are there separate facilities for the receipt and storage of test and control substances?
  - 5.2. Are there separate areas for the mixing of test substances with carriers?
  - 5.3. What written procedures for prevention of accidental cross contamination of test substances exist?
  - 5.4. Is access to stored test substances controlled?
  - 5.5. Are all test substances labelled to ensure their proper identification, storage and use (e.g. by expiry date)?
  - 5.6. Are there records of the receipt of the test substance, including identification, storage conditions, physical condition on arrival?
  - 5.7. Are there records of the utilisation of test substances?
  - 5.8. Are records of the identity, purity and stability of the test substance available?



- 5.9. Are mixtures of the test substance analysed for concentration, purity, homogeneity and stability?
- 5.10. Are there clearly defined standards for acceptability of analyses on mixtures (e.g. in the protocol)?
- 5.11. What arrangements exist for the prompt reporting of adverse findings on analyses of mixtures?
- 5.12. Are mixtures of the test substance labelled to ensure proper identification of test substance and concentration, storage conditions and stability (e.g. expiry date)?
- 5.13. Does the facility retain samples of test substances?
- 5.14. Does the facility retain samples of test substance mixtures, and, if so, for how long?
- 5.15. What procedures exist for disposal of test substance?
- 5.16. Does the facility have clearly defined standards for the handling of test substances (a) of unknown toxicity and (b) which are known to be hazardous?
- 5.17. Does the Study Director personally check the condition of the test substance?
6. Laboratory operations
  - 6.1. Are there separate laboratory operation areas for different activities sufficient to ensure the integrity of the operations conducted in the laboratories?
  - 6.2. Are there adequate procedures for the identification of samples and separation of activities to prevent accidental mix-ups?
  - 6.3. Are there adequate facilities for the retention of samples and records?
  - 6.4. If appropriate, are there defined environmental standards for laboratories?
  - 6.5. Are such environmental conditions monitored and recorded?
  - 6.6. Are reagents labelled to indicate their identity, titre or concentration, storage conditions and fitness for use (e.g. by expiry date)?
  - 6.7. Are there defined procedures for the cleaning of the laboratory both routinely and in the event of accident?
  - 6.8. Are there defined procedures to prevent illness or injury from exposure to hazardous materials?
7. Equipment
  - 7.1. Are all items of equipment used in support of the study of suitable design, capacity and location?
  - 7.2. Is equipment kept in a clean condition?
  - 7.3. Is there a person designated as responsible for each item of equipment, and is this clearly defined?
  - 7.4. What is the frequency, method and tolerance for checking the correct operation of equipment?
  - 7.5. What procedures exist for the routine and non-routine maintenance of equipment?
  - 7.6. What procedures exist to ensure that equipment which is unserviceable for any reason is not used?
  - 7.7. Are records of the checking, servicing and repair of equipment maintained?
  - 7.8. Are there defined methods for the use of equipment and steps to be taken in the event of malfunction or failure to meet tolerance?
  - 7.9. Is there an SOP for each item of equipment, available at the point of use of the equipment, covering points 7.3 to 7.8 above?
8. Manual data recording
  - 8.1. Are data recorded, directly, legibly and indelibly?
  - 8.2. Are all data signed and dated at the time of entry?
  - 8.3. Are alterations to data such that they do not obscure the original, and indicate the person making the alteration, the date of the alteration and the reason?

- 8.4. Is there an index of records, including location and responsibility, during the life of the study?
- 8.5. What procedures exist to protect the integrity of the data during the life of the study?
- 8.6. What procedures exist to ensure that the correct entry of data (or certain data considered to be individually 'critical') is verified?
- 8.7. Is there a definition of "original data"?
- 8.8. Are items 8.1 to 8.7 defined in SOPs?
- 8.9. Are there SOPs defining procedures for manipulation and calculation of data?
9. Computer generated data
- 9.1. What is the definition of 'original data'?
- 9.2. Are inputs identified by operator and date at the time of entry?
- 9.3. Are altered values identified and the original retained?
- 9.4. For alterations, can the operator, reason and date of alteration be identified?
- 9.5. Is there an audit trail which permits tracking of all changes from the original entry to the final output value?
- 9.6. Are the details of the system specification retained?
- 9.7. Is there a description of the hardware and software documented for the system?
- 9.8. Are there SOPs for the operations of the computer personnel?
- 9.9. Are there SOPs for the operation of the system by users?
- 9.10. Is there documented evidence of validation of the correct operation of the system, and does this define conditions under which the system may operate validly?
- 9.11. Are there documented procedures for change control?
- 9.12. Are changes to the operation of the system documented and retained?
- 9.13. Are there procedures for notification of faults and documentation of corrective action?
- 9.14. Are there procedures to prevent computer systems which are faulty or undergoing change being used before they are proven to respond validly?
- 9.15. Is there access control to prevent unauthorized changes to programs or data?
- 9.16. Are there procedures for back-up of data?
- 9.17. What data may be lost if the system fails accidentally, and how may these be recovered?
- 9.18. Do the requirements of section 7 (Equipment) apply to computer hardware?
- 9.19. What procedures exist for protection of data when computer systems are upgraded (e.g. can data recorded under earlier systems still be accessed?).
- 9.20. Has there been an assessment of compliance with Electronic Records and Electronic Signatures requirements?
10. Standard operating procedures
- 10.1. What is the procedure for production of SOPs?
- 10.2. What is the procedure for approval of SOPs?
- 10.3. What role does the QA function perform in the approval of SOPs?
- 10.4. Does an index of SOPs, including the title, author, and date of last amendment or review, exist?
- 10.5. Is there a historical record of all SOPs?
- 10.6. Who maintains the index and historical record of SOPs?
- 10.7. For how long are indexes and historical files of SOPs retained?
- 10.8. Are SOPs available at the point of use?
- 10.9. What procedures exist to ensure that the current version of the SOP is in use?
- 10.10. What procedures exist to ensure that staff are aware of changes to SOPs, and the requirements of the current version?
- 10.11. Is there an SOP or policy statement defining the production, approval and control of SOPs?

- 10.12. Is there a procedure for periodic review of SOPs, and at what intervals, and how is this documented?
  - 10.13. Is there a procedure for authorization of deviations from SOPs, and how are such deviations communicated to staff?
  - 10.14. Do SOPs exist for all routine procedures not covered in the protocol? SOPs should exist for at least the following:
    - (a) Receipt, identification, characterization, handling, formulation and storage of test substances.
    - (b) Testing of homogeneity and stability of test substance formulations.
    - (c) Administration of the test substance.
    - (d) Receipt, health checking and quarantine of animals.
    - (e) Identification of animals and other test systems.
    - (f) Care of animals and other test systems.
    - (g) Observations and examinations of animals and other test systems.
    - (h) Laboratory procedures and analyses.
    - (i) Handling of animals found to be moribund or dead.
    - (j) Autopsy procedures.
    - (k) Histopathology preparation and examination.
    - (l) Collection and identification of specimens.
    - (m) Field studies.
    - (n) Use of equipment for measuring or environmental control.
    - (o) Maintenance, cleaning and calibration of equipment used for measuring or environmental control.
    - (p) Use of computer systems.
    - (q) Data collection, handling, manipulation/calculation, storage and retrieval.
    - (r) Preparation of reports.
    - (s) Quality Assurance.
  - 11. Archives
    - 11.1. Are there archival facilities for the storage of all data and specimens generated during the study?
    - 11.2. Is there separation between wet and dry material?
    - 11.3. Are conditions controlled to prevent unnecessary deterioration of materials?
    - 11.4. Who is responsible for the archive?
    - 11.5. Is access restricted? To whom?
    - 11.6. What security measures (e.g. alarms) are used?
    - 11.7. Are magnetic media retained in archive, and what precautions are taken to minimize their deterioration (e.g. periodic respooling) if these are 'original data'?
    - 11.8. How are materials in the archive indexed?
    - 11.9. Are there SOPs for archival procedures?
    - 11.10. Are there cross-references to material archived elsewhere?
    - 11.11. Do retention times satisfy relevant regulatory authorities.
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## CHAPTER 18

# Report and Data Audits

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### 18.1 INTRODUCTION

The quality of data from clinical trials has significant implications for the Pharmaceutical Industry in the context of pharmacovigilance and marketing applications. It is unlikely that a regulatory authority would approve a marketing application without evidence that the study was conducted in compliance with good clinical practice (GCP) and that the data to support the application are reliable and complete. Ensuring data quality is an integral part of GCP, and sponsors are responsible for assuring the quality of data from their clinical trials. As such, many pharmaceutical companies have Quality Assurance (QA) departments specifically set up to maintain a quality management system for the clinical trial process. The quality management system may include audits of how study data are processed and how the results of analysed data are presented in the clinical study report (CSR). This chapter looks at approaches to auditing the management, processing and reporting of data generated from clinical trials.

### 18.2 THE QUALITY ASSURANCE FUNCTION

The purpose of a data audit is to assure confidence in the quality, completeness of integrity of the data. The scope of a data audit, and the extent and nature of QA activities, is often laid out in company policy statements, audit schedules or standard operating procedures (SOPs). For example, pivotal studies may be routinely selected for a data audit. In general, data audits are conducted before applying to the regulatory authority for a licence to market the compound. A data audit can focus on a specific study or programme, or look at the company's generic procedures that apply across all studies (systems audits).

To ensure that the audit is conducted in an unbiased and objective way, the auditor should be independent from the persons directly involved in the conduct of studies, including the clinical team, data management and the medical writing team. It can be particularly difficult for small companies to maintain true QA independence, where staff have dual roles in QA and clinical projects and/or data management.

### 18.3 PREPARING FOR THE AUDIT

#### 18.3.1 The Audit Plan

Having clear ideas about what is to be accomplished from the audit and how to achieve the objectives is central to any type of audit. Data audits are no different, and having a properly

thought-out audit plan is a good place to start. Data audits encompass the following four separate areas:

- The data management system
- The database
- Validation of the computer system
- The clinical study report.

Each of the four areas mentioned above can be considered as a separate audit. Some auditors may choose to combine one or more areas, for example combining a database audit with either a data management system or a computer systems validation audit. For the purpose of this chapter, the four areas are considered as separate audits.

Regardless of which of the four areas are audited, the objective is to assess the compliance of activities with GCP, applicable international and local regulatory requirements, SOPs, contractual requirements (if applicable) and the study protocol (if the audit is part of a study-specific exercise). The audit plan should outline the objectives of the audit, and how you will achieve the objectives. Assessments of compliance can be made through the following ways:

- Interviews with relevant staff
- Review of documentation
- Review of facilities
- General observations
- Review of SOPs and policies
- Review of training records.

The Audit Plan should give a detailed account of the scope of the audit, what will be assessed and the specific auditing activities that will be performed to make assessments. The standards to audit against should be clearly defined. For example, a data management system would be assessed for compliance with ICH GCP, FDA Codes of Federal Regulations (21 CFR) and relevant SOPs. SOPs may be assessed for compliance with ICH GCP, as well as the adequacy of the SOPs for the purpose intended.

The contents of the Audit Plan might include:

- Brief details of the study to be audited
- Objectives of the audit
- Scope of the audit
- Approximate timelines for the preparation, conduct and reporting of the audit
- Selection criteria to be used
- Outline of specific auditing activities that will be conducted during the audit
- Auditing standards (SOPs to be used and regulatory documents to be referred to)
- Reporting procedures
- Responsible auditor(s) and contact details
- Contact details for relevant clinical study team members including CRO contacts if applicable.

The extent and nature of sampling of data for audit should be defined in the Audit Plan, for example the number of CRFs to review against the database listings and whether all data points on the selected CRF will be checked. Other examples of where sampling may apply are in the selection of parameters, such as primary efficacy variables and serious adverse events (SAEs), and whether these are included across all subjects or for selected subjects.

### 18.3.2 Checklists and Worksheets

A checklist or worksheet can be a useful tool to record information gathering during the audit. The key to designing a useful worksheet or checklist is to make sure that it reflects the items details in the Audit Plan. The auditor should form clear ideas of what information is needed and why. The type of worksheet used may depend on company policy and/or the preference of the individual auditor.

### 18.3.3 Notification of the Audit

Auditees should be contacted soon after being selected for audit to notify them of the audit and to make the necessary arrangements. The auditor may contact the auditee directly, or this may be done *via* a facilitator, depending on the preference of the sponsor or organisation. For a routine audit, it is reasonable that the auditee receives adequate notice of the audit in order to prepare, and to ensure that the relevant documents and staff are available on the day. Around 2 or 3 weeks notice would be appropriate in most cases.

Once a mutually convenient date for the audit has been agreed, the auditor should confirm this with the auditee in writing. It is not difficult to see the attraction of providing the auditee with an agenda, detailing what the exact requirements for the audit are, what it will entail and which staff are to be interviewed. This helps the auditee to organise work schedules and ensures that all of the items and staff needed for the audit will be available. Providing the auditee with an audit agenda will go a long way towards making the audit proceed smoothly and efficiently.

There are certain information and documentation that may be helpful for the auditor to receive prior to the audit:

- Contact details of the auditee: Name of key contact person(s), telephone and fax number, location of the facility
- An organisation chart or list of relevant staff involved
- Copies of relevant SOPs, or a list of SOPs
- A copy of study-specific documents: Protocol and Amendments, Investigator Brochure, blank CRF, statistical and data management plans, details of the study status and recruitment.

## 18.4 AUDIT CONDUCT

There are auditing activities common to all types of audits. These include:

- A review of the quality system, SOPs, relevant documentation, staff training records
- Conducting interviews.

An effective quality system, comprising QA and quality control (QC) activities (Chapter 9), should be in place to ensure compliance with standards and the completeness, consistency and accuracy of data. SOPs can be considered as part of the QA system.

The Auditor should ask for SOPs to be made available for review. Comprehensive SOPs should be in place for each activity and process, including the management, writing, review and approval of SOPs (as discussed in Chapter 3). Individual SOPs should be adequate for the intended purpose, be approved at an appropriate level of seniority and be up-to-date. Distribution and recall of SOPs should be controlled and documented.

Documentation should be audited for internal consistency, consistency with other documents, completeness, accuracy, appropriate version control, dates, and signatures at the appropriate level of authority. Where documents have required translation there should be documented evidence of appropriate translation procedures, for example suitability of the translator's qualifications and history of translation.

As discussed in Chapter 39 training records should demonstrate that staff are suitably qualified and trained for their roles and responsibilities. Evidence of formal training should be documented, commonly in the form of training records. As a minimum, staff should be trained in the relevant company SOPs and policies, and GCP.

Much information can be gathered from interviews with relevant staff. Detailed descriptions of how individual staff perform specific tasks on a day-to-day basis can be obtained. Interview techniques largely depend on the preferred approach to the individual auditor. It is worth bearing in mind during interviews that staff might have been instructed to volunteer only the specific information asked of them, and nothing more! Therefore, use of open questions and, where possible, review of documentation to support the interview, should allow the auditor to establish what the current practices are.

## 18.5 AUDITING THE DATA MANAGEMENT SYSTEM

An audit of the data management system encompasses a review of the many procedures involved in the data handling process, from receipt of data, for example CRFs, by the sponsor or CRO, through to transfer of the processed data ready for statistical analysis. For a study-specific audit, the audit would commonly be conducted while the study is ongoing or has just completed. The timing of the data management audit may be after a predetermined number of CRFs or data points have been processed.

When study data are received at the sponsor or CRO site, data are usually subject to various handling procedures such as photocopying, distribution for review coding, data entry, query generation, filing and storage, to name but a few. The system used to track data is an important area to audit.

Items for audit should include but may not be limited to:

- Data management department organisation and reporting structure: Communication and information dissemination (*e.g.* regular meetings with minutes)
- Staff roles and training
- Current processing capacity (*e.g.* how many CRFs can be processed per week. CRFs may be processed in batches)
- QC procedures should be in place for each step of the data management process
- Data receipt, transfer and tracking procedures (*e.g.* CRFs)
- Methods and procedures for data entry (*e.g.* single or double data entry)
- Generation, tracking and resolution of data queries and integration of resolved queries
- Coding methods and dictionaries used
- Data editing procedures and audit trails for changes made
- Randomisation and unblinding procedures
- Adverse event report and tracking
- Database locking and unlocking procedures
- Document handling and tracking procedures
- Archiving of documents, including CRFs data listing.

### 18.5.1 Review of Documentation

*18.5.1.1 Standard Operating Procedures.* The auditor should ask for SOPs to be made available for review. Comprehensive SOPs should be in place for each step of the data management process, as listed above.

A data management plan is often generated to document study-specific requirements and activities.



**18.5.1.2 QC Records.** An effective QC system should be in place and there should be documented evidence of QC activities for each step of the data management process. A review of the source QC records can assess the QC process and whether appropriate action was taken as a result of discrepancies identified from QC reviews.

When auditing QC records, the auditor should consider the methods, scope and extent of QC activities, as defined in SOPs or study-specific instructions. For example, SAE and primary efficacy data may undergo 100% QC checks, while random QC checks on a sample of laboratory and concomitant medication data may be performed.

Checks should include what QC checks were actually performed, by whom and how the QC checks were documented. To compensate for data that is not selected for QC, and for errors that can never be detected or easily identified, an acceptable error rate is commonly defined. For individual studies, certain data may be pre-defined as critical, for example serious adverse events, or non-critical, for example noncomitant medication. The extent of QC checks performed may depend on whether the data are critical or non-critical, for example 100% QC checks for critical data and 10% for non-critical data.

Acceptable error rates vary between companies and may be 0% for critical data and up to 0.5% for non-critical data. Should the error rate be exceeded, then the recommendation would be to perform full QC checks on 100% of the data.

QC records may be in the form of manual worksheets and checklists or computer generated logs and reports. Listed below are a few examples of how QC checks may be documented:

- Visual checks on data coding may be directly annotated on the printouts of records generated from the database.
- Visual QC checks of CRF *vs.* database listings may be annotated on the printouts of the database listings.
- Printouts of automated check programmes that are run to compare the results of double data entry.
- Printouts of the records or logs of the edits made to the database, giving an audit trail of what data was edited, when, by whom and why can be reviewed.

## **18.5.2 Source Data *vs.* Database Comparison**

The data stored in the database should accurately reflect the original source data, for example CRFs. A direct comparison of a sample of CRFs and data queries against the database listings can be made. The sampling of CRFs for audit may be based on a per cent of the number of CRFs entered into the database, for example  $\sqrt{x} + 1$  (where  $x$  = the number of CRFs entered into the database).

## **18.5.3. Review of Facilities**

The auditor should take the opportunity to inspect the relevant facilities. When touring the facilities, consideration should be given to the physical security equipment for buildings, offices and computer areas, for example protection from theft, fire and flood.

In addition, the areas for data entry, document storage and archiving should be visited. Documents should be kept separately from eating areas and be stored in a secure area, for example locked room or cabinets.

## **18.6 AUDITING THE DATABASE**

When auditing databases, the focus should be on the database itself and the data stored in it. Consideration should also be given to how data is transferred between systems, for example from a

clinical database to a statistical or safety database and *vice versa*. All audits should follow the principle that quality is built up-front. Therefore, to establish that a working QC system is in place, it may be necessary to audit the database at an early or middle stage of a study. This allows corrections to be made. Of course, not all data will be complete or accurate, but it may highlight real or potential problem areas.

Similar to a data management audit, part of the assessment of the database should be made through interviews with relevant staff, documentation review and general observation.

A lock of the database is usually performed to prevent any further change to the database prior to transfer of the data for statistical analysis. Procedures for locking and unlocking the database and changing data should be strictly controlled, and procedures are usually defined in SOPs.

Before the database is locked, a final data QC check is performed on data that is considered to be “clean”, for example when no outstanding queries or discrepancies remain. The definition of “clean” data may vary between companies and even studies. The definition should be documented before the database is locked.

Security of the database should be assessed. Physical security measures should be in place, for example building alarms, protection from fire, flood and theft, restricted access to the computer area and to the database. A system or device should be installed that affords the database protection from interruption or surges of the power supply. Logical security measures may include password protection and restricted access to the database, current virus protection for computers and servers, separate servers for Internet and e-mail.

Frequent backup of data should be done on a daily, fortnightly and monthly basis. Backup media should be stored securely and separately from database servers. Records of backups should be reviewed.

Disaster recovery procedures should be in place to ensure that data can be recovered in the event of a major disaster or system failure. The recovery procedure should ideally be tested by performing a full data recovery exercise at least once during the active life of the database.

Further guidance on use of computers is given in Chapter 37.

### 18.6.1 Database Design and Structure

The design and structure of the database should comply with the project specifications and the auditor should consider the following items:

- Whether the database was designed and built in-house
- Whether off-the-shelf software packages were used and if these were modified
- QC checks for statistical and analytical programmes
- Programming standards
- Audit trail
- IT support and computer system maintenance
- Technology used (*e.g.* workstations, file server networks)
- Technology maintenance and support. Maintenance records should be reviewed
- Screen setup, including screen savers
- Data set formats and titles. Whether screens are set up to reflect the CRF and whether screens can be compared
- Data export and import. Establish what format and medium is used for transfer, for example American Standard Code for Information (ASCII) file stored on diskette, tape or sent by e-mail; encryption procedures; interfacing with other computer systems
- Arrangements for long-term archiving of the database and format used
- Data-handling conventions used
- Definition of a data item (*e.g.* is the date a single item or three items)

- User Manuals or Instructions for use
- Problem reporting, change control
- Training on the system(s)
- Use of electronic signatures, if applicable.

## 18.6.2 Documentation Review for the Database Audit

*18.6.2.1 Standard Operating Procedures.* The auditor should ask for SOPs to be made available for review. Comprehensive SOPs should be in place for each of the items listed above.

*18.6.2.2 Project-specific Documents.* All project-specific documents generated for the conduct of the study may be subject to audit, including database specifications, data management plan, project manuals, protocol and amendments.

*18.6.2.3 QC Records.* As for the data management system audit, covered in Section 18.5, the following QC documentation should be reviewed:

- The methods, scope and extent of quality control activities, as defined in SOPs or study-specific instructions
- What QC checks were actually performed, by whom and how the QC checks were documented
- The acceptable error rate and pre-defined critical and non-critical data.

Multiple computer systems may be used to handle, process and analyse data, for example a clinical or CRF database that originally captures data and a statistical database that further processes and analyses the data. A typical scenario is where analysis programming produces basic table shells, ready to receive data from the clinical database. Data from the clinical database is then uploaded into the statistical database. For example, SAS is a widely used statistical tool and uploading of data can be done *via* an SAS interface option that allows transfer of data between systems. The statistical databases then produced data sets and listings, according to the Analysis Plan. An independent statistician or programmer will commonly perform QC checks on critical aspects of database output, programming and log files. The auditor should review the documentation of the QC checks performed.

To ensure that the data between systems is consistent and data transfer has been successful, the data produced from each system can be compared. For example, data listings produced by the clinical database can be compared to the listings from the statistical database. Statistical summary tables can be audited for consistency with the statistical and clinical database listings.

The extent of the tables and listings review should be defined before the audit commences. It would be expected that QC checks would already have been performed, and that discrepancies should fall within the accepted error rate. Therefore, the approach to the audit should be from a QA perspective, rather than a QC exercises.

A statistical database produces summary tables and as part of the QC process, the summary tables and derived data sets may undergo a complete review, that is the programmes will be rewritten and run by different programmers.

## 18.6.3 Source Data vs. Database Comparison

The first data listings from the database are commonly produced when all data is entered and all queries are resolved. As for the data management audit, a direct comparison of the source data and resolved data queries against the database listings can be made. To do this 100% would be

time-consuming and unnecessary if adequate QC steps are implemented. As such, many companies take a sample of CRFs and data queries and compare these 100% against the database listings. The sampling of CRFs for audit may be based on a percentage of the number of CRFs entered into the database or an arbitrary statistic may be used, for example  $\sqrt{x} + 1$  (where  $x$  = the number of CRFs entered into the database).

#### 18.6.4 Review of Facilities

The auditor should take the opportunity to inspect the relevant facilities. When touring the facilities, consideration should be given to the physical security equipment for buildings, offices and computer areas, for example protection from theft, fire and flood. In addition, the areas for data entry, document, storage and archiving should be visited. Documents should be kept separately from eating areas and should be stored in a secure area, for example locked room or cabinets.

### 18.7 AUDITING THE VALIDATION OF COMPUTER SYSTEMS

The use of computerised systems for handling clinical trial data is increasingly widespread in the pharmaceutical and related industries. Computerised systems can shorten timelines for data processing and analysis, give low error rates for data accuracy and streamline production of Clinical Study reports. These are all vital advantages for profitability in today's competitive market.

Types of computer systems that may be included are:

- Interactive voice recognition systems
- Clinical databases
- Statistical databases
- Laboratory databases and Information Management systems
- Electronic CRFs and remote data entry (RDE)
- Direct data capture (DDC) systems that centrally capture and manipulate data into a single standard
- Automated measuring equipment
- Bar coding equipment
- Optical imaging
- Electronic patient medication packs that automatically track patient compliance
- Document management and assembly systems
- Adverse event tracking systems
- Project management and communications systems to co-ordinate RDE, trial management, monitoring and reporting.

To assure the accuracy and integrity of data, the computer system used to generate, process and analyse the data should be fit for the purpose intended. Documented evidence should demonstrate that the computer system was designed, developed, implemented, operated, maintained and retired/decommissioned in a controlled manner and produced the intended results. In other words, the system is shown to be validated.

The objective of the computer system validation audit is to assess the compliance of the system with national and international regulations and guidelines, and company SOPs covering these aspects.

#### 18.7.1 Regulations and Guidelines

The regulatory requirements for the validation of electronic systems are detailed in ICH GCP 5.5 and the US Food and Drug Administration (FDA) Code of Federal Regulations for Electronic Records and signatures "Rule 21 CFR Part 11". The FDA has also issued guidance notes for the

use of electronic data, “Guidance for Industry: Computerised Systems Used in Clinical Trials”. There are also other guidance documents. In addition, “*A Practical Guide: Computer Systems Validation in Clinical Research*” is published by the Association for Clinical Data Management and Statisticians in the Pharmaceutical Industry (ACDM/PSI).

The essence of the FDA requirements can be summed up in the statement “persons using the data from computerised systems should have confidence that the data are no less reliable than data in paper form”.

### 18.7.2 Computer Systems Development

There are six main phases of a computer system’s life cycle, from conception to retirement and archiving. Each phase of the life cycle should be validated.

- Planning
- Designing: Specifications of what the system is intended to do and produce
- Building: How the system is built to fulfil the required specifications
- Testing: What QC activities were performed on the system to ensure that it produces the expected result
- Release of the system
- Retirement and archiving.

### 18.7.3 Items to Audit

The co-ordination of multi-disciplinary teams of users, programmers, management and IT support teams would be required to co-operate to fulfil all of the requirements of validation. The auditor should establish the reporting structure and methods of communication between the teams. CVs and training records of the relevant key staff should be reviewed to assess whether staff are suitably experienced and trained for their roles. Documented evidence of training in GCP and SOPs should be available.

The starting point for the audit can revolve around the SOP dealing with the inventory of systems. This list should detail all the systems in place/use in the company/department including the current operating version. For each system the auditor should request the system overview document. This will provide information about the system such as when was it last validated, the user manuals, SOPs, contacts/owners, *etc.* Once the auditor has determined which systems to audit they should request the relevant SOPs and documentation to support the system. Many companies store validation documentation in the validation package, which should be archived once the system has been placed in the live environment. Once a system has been placed in to the live environment there should be a process of change control to manage any changes that need to be made to the system. Change control procedures should be fronted by a problem reporting/bug fixing service, which allows users, including developers to report parts of the system which are not functioning.

To assess the validation activities, the auditor should start with the validation plan or protocol. Depending on the type of company and system there may be one validation plan or many. The validation plan should cover all areas of the system which need to be designed, built, implemented, maintained and retired. This includes, but may not be limited to the audit trail, backup and recovery, user training, user manuals, source code preparation, QC, testing and release, installation. All of these areas should be considered in the Validation Plan. Any areas being considered outside of the scope of the validation should be documented with explanation added as to the decision made. A risk assessment should be detailed which again details any areas which may be considered outside of the scope of this particular system’s validation. The criteria for accepting the system before it is released for use should be documented.

The final deliverable from validation is the validation report/release report. This document should detail what was done in the validation activities, the outcome and if the system is ready for release. An adequate level of authority for release should be established.

As with other areas, QC functions should be evident and the methods of testing should be defined and documented. The auditor should review QC documents that record the checks performed, the outcome of the checks and actions taken.

Automated randomisation methods should be documented and the auditor should assess whether the randomisation procedures have been performed according to the study protocol and SOP requirements.

Use of hardware and software development should be defined and documented, and an inventory should be kept.

The source code (computer programme written in human readable form, which is translated into machine readable language) and historical versions should be available and appropriately controlled. It is not necessary for the auditor to understand the source code, but a computer programmer may be asked to explain this, if required.

The installation and updates of operating systems, layered products and applications should be documented. The documentation that records the tests performed, the outcome of testing and actions taken should be reviewed to assess whether installation and updating of operating systems has been successful.

Programming standards and testing should be defined and documented. Programmers may initially perform testing on their own work before the programme is subject to a QC check.

Change control for changes to hardware and software operational procedures should be documented. Version control of software and operating systems should be appropriate and documented. Change control procedures should be defined in SOPs.

Use of electronic signatures should be compliant with FDA 21 CFR part 11, which requires strict control and documentation of the use of electronic signatures. Security, Backup procedures and Disaster recovery procedures should be adequate, as discussed in the above Section 18.6, Auditing the Database.

Archiving arrangements should be adequate and documented: On-site and off-site storage and transport of electronic storage media should be defined. It is important to establish what format the data will be stored to ensure that the data can be read, if needed, in the future.

Authorisation for release of the system should be documented. Authorisation for release should be made at the appropriate level of seniority.

#### **18.7.4 Documentation Review**

*18.7.4.1 Standard Operating Procedures.* The auditor should ask for SOPs to be made available for review. There should be SOPs in place for each step of the validation process, from design to archiving.

*18.7.4.2 System Validation Documents.* The following documents should be reviewed:

- System Inventory
- System specifications/overview: Defines what the requirements of the system are and what it is intended to produce
- System development plan: How the system is to be built to achieve the specifications
- Validation plan: What validation and testing was intended
- Records of validation checks and tests: Records of checks and tests performed and the outcome of testing. This includes testing of computer programmes and testing done by the end-users of the system in the actual working environment
- Authorisation for release of the system.



### 18.7.5 Causes of Validation Failure

There are many reasons why validation of a system fails. Some common causes include inadequate documentation of planning and the definition of what constitutes the system, specification of software and the definition of expected results.

The source code for computer programmes and historical versions of the source code may not be available or be adequately controlled. The source code should be kept in a secure place with restricted access. The ownership of the source code may be an issue to some companies, if this was generated by a CRO.

The software may not meet the specifications. The performance and end product of the software should reflect the intended purpose.

A common audit finding is a lack of adequate change control and revalidation whenever a change occurs that exceeds operational limits or design specifications. If any major changes are made to functional programmes, software or operating systems, then revalidation should be performed. The extent of validation and the testing done should be documented. If a change is minor and affects only part of the system, then revalidation of the relevant area only may be performed. Any modification of customisations to the system should be validated, including any customised programmes written in a package's native programming language. Change control and how it is effected should be detailed in an SOP.

Responsibility of contractors may not be adequately defined (*e.g.* companies installing a system, IT contractors, validation consultants, *etc.*). Formal contracts may not even exist.

Testing of off-the-shelf products may not be deemed necessary by the user of the system. Validation should be done to ensure that the system works within the specific environment in which the system is operating. It would be expected that even minimal checks are made to document that the product is suitable for the intended purpose.

The extent of testing may be inadequate, or not adequately documented. All testing done, the outcome of testing and remedial actions taken should be documented.

Inadequate documentation of user requirements or changing user requirements.

Infrastructure for support may not be present (*e.g.* user manuals, help desk). This may be particularly relevant for studies using RDE or automated interactive voice recognition systems.

Staff training or documentation of training may not be adequate. Staff should have documented evidence of training in the relevant functional areas, SOPs and GCP.

### 18.7.6 Review of Facilities

The auditor should take the opportunity to inspect the relevant facilities. When touring the facilities, consideration should be given to the physical security equipment for buildings, offices and computer areas, for example protection from theft, fire and flood. In addition, the computer, document, storage and archiving areas should be visited. Documents should be kept separately from eating areas and be stored in a secure area, for example a locked room or cabinets.

## 18.8 AUDITING THE CLINICAL STUDY REPORT

A description of the study, the statistical methods used and an interpretation of the results are integrated into a CSR. The CSR forms part of the marketing application to the regulatory authority. The object of a CSR audit is to assess whether the report is a fair and accurate account of the study and the submitted data, and complies with ICH, regulatory requirements and SOPs.



### 18.8.1 Regulations and Guidelines

Standards to audit against are the ICH Notes for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH 137/95). These ICH guidance notes define how clinical reports should be structured and what the nature of the contents should be.

### 18.8.2 Documentation

Relevant documentation and information should be requested prior to the audit, or be made available on the day for review:

- Protocol and amendment(s)
- Investigator's brochure
- Blank CRF
- SOP on writing/compiling a CSR and other relevant SOP(s)
- CSR to be audited, complete with all appendices, listings, tables and figures
- Description of the QC checks performed and documentation to support this
- Confirmation that the database was locked prior to the production of the CSR.

### 18.8.3 Review of the Clinical Study Report

The review of the CSR should verify that the document meets the following criteria:

- Complies with applicable regulatory requirements
- Adheres to CPMP/ICH Note for Guidance on Structure and Content of Clinical Study Reports (CPM/ICH 137/95)
- Adheres to the relevant SOPs
- Accurately reflects the study protocol, CRF and study-related documents
- Is an accurate and complete summary of any raw data listings, and is clear and consistent throughout all sections.

The structure and content of the report should be compliant with the CPMP/ICH/137/95 and with the relevant SOPs. The structure, content and summary section of the CSR should be accurate reflection of the body of the CSR. The report should also be consistent with the protocol and any amendments. This will include whether:

- The objectives of the study are consistent and any changes are explained
- The efficacy and safety parameters stated in the protocol were measured as stipulated
- Any deviations from the protocol are explained
- The statistical analyses reflect the analyses stated in the protocol
- All changes are documented, including timings and approvals
- The randomisation code has been accurately assigned to the subjects.

The report conclusions should be an accurate representation of the results, including statistical analyses.

Additional items for the auditor to consider may be the following:

- The text for clarity, ease of reading, grammar and typographical errors
- Pagination is complete and sequential
- All dates are in an unambiguous form
- Review procedures for signing and approving documents
- Review of any QC documentation
- Review of any applicable audit reports and certificates if appropriate.

#### **18.8.4 Appendices**

The content of the appendices should comply with ICH guidelines. The auditor should check whether all of the appendices have been provided, documents are complete and referenced appropriately in the table of contents. For example, details of the Investigator Sites and Ethics Committees are included in the appendices. Tables, listings and figures also form part of the appendices.

#### **18.8.5 Auditing Tables, Listings and Figures**

A comparison can be made of tables and figures, and other data mentioned in the report, with statistical summary tables and/or raw data listings in the appendices. Tables and figures should be referenced appropriately.

The extent of the tables and listings review should be defined before the audit commences. It would be expected that QC checks would already have been performed, therefore, the approach to the audit should be from a QA perspective rather than a QC exercise.

Sampling is often used to select tables and listings for audit, depending on the nature of the data and how the data is presented. For example, adverse event data may be selected for audit and for a small study, all of the adverse event data for all subjects may be checked 100%. For a large study, a percentage of the total number of subjects may be reviewed 100%. Similarly, 10% of concomitant medication data may be checked. There are no clear standards and guidelines for sampling data for audit. Suffice to say that if the accepted error rate is exceeded, then consideration should be given to rejecting the data and recommending 100% QC checks or reanalysis, bearing in mind the QC system itself may be the root cause of the discrepancies!

The following should be considered when reviewing tables and listings:

- Check whether all tables and listings have been provided
- Tables and listings are referenced appropriately and sequentially. Particular attention should be made to correct titles and footers
- Summary tables are consistent with raw data listings
- The listings and table produced from different databases are consistent
- All of the subjects and events that were analysed have been included in the tables and listings.

### **18.9 POST-AUDIT ACTIVITIES**

#### **18.9.1 The Close-Out Meeting**

Following completion of the audit, a close-out meeting should be conducted with the auditee to feed back on the main observations made during the audit. The auditor should allow time to prepare for the close-out meeting to identify what items need to be discussed and any clarification that is required.

The feedback on audit findings should be constructive and be beneficial to both the sponsor and the auditee. The auditor should document the responses given by the auditee during the close-out meeting. The auditee should be informed of the audit reporting process, timelines and how the auditee should respond to the findings.

Audit findings may be critical in nature, for example an unacceptable departure from GCP guidelines/regulations has compromised the integrity and credibility of some or all of the data. This may affect the suitability of the data for regulatory purposes. If critical issues are identified during the audit then the appropriate staff within the organisation should be notified by the auditor as soon as possible so that swift action can be taken to rectify the problem. Notification can be made via fax, e-mail or in writing.

### 18.9.2 The Audit Report

The audit report should be written soon after completion of the audit as possible. The timelines for producing reports, content, style and format vary between organisations. When designing an Audit Report template, the following should be considered:

- The type of audit, study title and protocol number, audit date(s) and location(s).
- Summary, providing an overview of the audit and the most important audit observations. This may be useful where the report will be reviewed at a managerial or executive level.
- Introduction to the audit giving details of the objectives, scope, areas audited, staff interviewed and standards used to audit against.
- Observations: Individual observations should be given a unique identifier, so be clear and unambiguous. Consideration should be given to classifying observations as ‘Critical’, ‘Major’ or ‘Minor’.
- Some organisations require the auditors to make recommendations for corrective actions, while some prefer the clinical teams to decide on what actions should be taken. If recommendations are made, the auditor should try to provide the most feasible and pragmatic solutions that are right for the situation.
- Summary of the close-out meeting discussions.
- The audit report should be signed and dated by the author.

In some organisations, provision for written responses to the audit observations is given in the report, and in others, the study team produces a separate action plan.

Authorised persons only should have access to the information within the report. The distribution of numbered copies of audit reports should be limited to designated people and photocopying should not be encouraged.

### 18.10 CONCLUSION

Data audits are similar to audits in general, with assessments made by way of interviews with relevant staff, documentation reviews and observation. The focus of the audit should be on the overall process, the quality system and compliance with GCP, national and international regulations and SOPs. The success of an audit should be measured in terms of the extent to which compliance has been demonstrated and how actions taken as a result of the audit achieve compliance and improve practices.

An auditor need not be a computer expert or statistician to conduct a data audit.

## CHAPTER 19

# Quality Assurance and Contract Research Organisation: GLP Studies

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## 19.1 INTRODUCTION

Why do Sponsors contract out regulatory work that needs to be conducted according to Good Laboratory Practice (GLP), and what makes them choose a particular contract research organisation (CRO)?

There are common reasons for outplacement of GLP work such as a lack of internal capacity or capability, through well-defined minimum time-to-market strategies to the ‘virtual’ company that simply has no choice to make. Once the choice to outsource is made, however, the choice process is only beginning. Which CRO will be chosen, and why? Many factors will be taken into consideration – familiarity, availability, location, timings and cost are obvious, but corporate politics and the ‘old boy network’ can often play their part too. Perhaps the soundest reasons for choosing one particular CRO over another are those of reliability, quality and compliance – and here the CRO’s Quality Assurance (QA) function has a tremendous role to play. QA is assuring quality in the broadest possible sense.

This chapter sets out to highlight the peculiarities of GLP QA in a Contract Research environment and to explore how the QA function adds value to the business.

## 19.2 RESPONSIBILITIES UNDER GOOD LABORATORY PRACTICE

The OECD GLPs (ref. 1) lay out the responsibilities of Management, Study Directors, Principal Investigators, Study Personnel and QA in very clearly defined sections within the main text of the GLP Principles themselves. The overarching responsibilities of Sponsors are dealt with separately in the OECD’s series on the Principles of GLP and Compliance Monitoring, appearing as an advisory document at No. 11 (ref. 2) in the series. Also in the same series of OECD documents are consensus offerings on the Role and Responsibilities of the Study Director,<sup>3</sup> Suppliers<sup>4</sup> and, reassuringly, QA.<sup>5</sup>

With such an array of available guidance, is there really scope for further interpretation and guidance? Do not the regulations themselves already have enough to say about the role and responsibilities of QA? Actually, the beauty of working in a CRO and functioning as the service provider in an infinitely variable customer service relationship means that the answer to those questions becomes immediately obvious; despite the fact that is often embodied in law, GLP is actually a principle, a guide, a framework and as such is almost infinitely interpretable. “Two hundred and fifty-six shades of grey” does not really do the flexibility of GLP justice, but one does

begin to see the possibilities. The principles of GLP are certainly well established, having been in existence for almost thirty years, but the application of those simple principles to an ever-increasing range of environments allows an amazing scope for variation.

Sponsors have a duty to monitor the scientific quality of work being conducted on their behalf and this duty also extends to having an opinion on the GLP compliance of contracted work. The consequence, in a Contract Research environment, is that the fundamental regulations often take something of a back seat in relation to an individual's opinion when it comes to keeping Sponsors delighted with their choice of CRO. It has been said that the Sponsor is never wrong – misguided, over-demanding, unhelpful, unreasonable, late with its contribution – but never wrong! Of course, this is a very jaundiced and hackneyed view. A very small percentage of Sponsors fall into this category while the vast majority work very hard at developing and maintaining an open, honest, reasonable and constructive relationship with their CRO of choice. Nevertheless, the CRO QA philosophy has to include both flexibility and pragmatism in order to maintain sustainable levels of compliance in the face of such diverse external input into a facility's quality systems.

Probably the single biggest issue in the interpretation remains the question of "Quality Assurance or Quality Control (QC)" What do the terms mean and where do the boundaries lie? Again, the regulations themselves really do not help that much, though the fundamental requirement for GLP QA to be 'independent' certainly gives a clue. Essentially, QC systems and processes should be owned and implemented by Management – the Independent QA function simply monitors to verify that appropriate QC systems are operating effectively. An established CRO QA will have very robust ideas on where those boundaries lie in their own organisation and can be expected to defend them.

### 19.3 CONTRACT RESEARCH ORGANISATION CHOICE

A sponsor electing to contract out GLP work for the first time will be confronted by a very wide choice for most regulatory studies. CROs come in all shapes and sizes, from the niche player offering a single product line and having just one or two permanent staff to the large multinational full-spectrum players with thousands of staff, scientific experience to die for and regulatory pedigrees stretching back to the very birth of GLP. In many countries, including the UK, there is a legal requirement to conduct GLP studies in 'certified' GLP facilities; in others, including the USA, the situation is more flexible and a facility may conduct GLP work before any formal regulatory inspection occurs.

In any event, the Sponsor has a real duty to ensure that the facility they chose has a genuine basis on which to make a formal claim of compliance with GLP at the end of a study. The level of assurance that a Sponsor may seek before placing work varies tremendously, and the possibilities are endless. Anything more than a very simple and direct 'Are you GLP compliant?' question, which would normally be answered correctly by the sales or marketing function, will probably be directed to the QA team for a detailed response. Such requests for information (RFIs), can be quite straightforward but they can also be extremely demanding. Many will be questionnaires based on the GLP regulations, or a hybrid of GLP, good manufacturing practice (GMP) and good clinical practice (GCP) – even non-regulatory quality systems such as ISO 9000 – and require careful interpretation and response. In fact, these one-size-fits-all questionnaires can turn out to be quite misleading if the language of non-GLP regulations is used. For example, such a questionnaire based on GMP and asking about QA systems poses a sticky trap if the responder does not realise that GMP QA activities *include* QC processes, self-inspection activities and technical approval and release processes as well as independent audit, whereas GLP QA is strictly independent audit only.

Questions will vary from very simple enquiries about the existence of Standard Operating Procedures and other essential GLP programme requirements, through QA staff numbers and their depth of experience to complex assessments of technical capabilities. The numerical ratio of QA to other staff often comes up as an item for response but there is no magic answer – anything in the

range 1:15 to 1:30 is common, and higher ratios may well be quite acceptable in an automated or highly established environment. The important thing is to be able to demonstrate that QA is operating effectively rather than efficiently at this stage. Inevitably, the Sponsor will ask to see real evidence of genuine GLP status including copies of compliance statements issued by national Inspection Authorities and even copies or transcripts of recent regulatory inspection findings. Just being given the chance to bid on multi-million pound packages of work can depend on acceptable responses to these RFIs, and so the potential to fail the selection process at this early stage can put considerable pressure on QA.

## 19.4 SPONSOR INPUT AND RESPONSIBILITIES

Despite guidance from the OECD,<sup>2</sup> and in particular with reference to multi-site studies, Sponsor input remains extremely variable. Pre-placement audits vary from no activity at all to multi-personnel multi-day on-site inspections; ongoing monitoring of studies also varies from zero presence to attendance and parallel inspection at the majority of critical phases, through to a complete re-audit of the draft final report. Similarly, communication varies from total silence to regular, free and frank exchanges of information. The CRO is often left feeling their way with new Sponsors and may only settle into a comfortable pattern when a number of studies are completed and a relationship is established.

Although there will certainly be contractual obligations placed upon a CRO to perform work in compliance with GLP, all Sponsors should be aware of their own responsibilities. Recent personal experience in face-to-face discussions with a receiving authority while they reviewed a pivotal study confirmed that the Sponsor is certainly expected to have gained first-hand knowledge of both scientific interpretation and GLP compliance and not simply rely on the CRO's reported position. Although National GLP Inspection Programmes effectively underwrite the compliance claims in individual studies and the OECD's Mutual Acceptance of Data scheme eases the passage of overseas studies at registration, receiving authorities clearly reserve the right to challenge Sponsors directly when they feel it necessary.

## 19.5 THE QA PROGRAMME IN A CRO

Depending on the size and throughput volumes of a CRO, the QA function can be as small as a part-time or shared role through to a dedicated team of well over 50 staff organised into a structured department. Especially in the smallest organisations, it is not uncommon to find at least some QA resource provided by external contractors or consultants, many of whom have a great deal of experience and may even have been established QA managers earlier in their careers. One of the fundamental tenets of GLP QA is that the auditors gain a reasonable level of familiarity with the work they are required to audit and thus the training programme in QA needs to reflect the volume, variety and complexity of work on offer in that CRO. Some larger CROs will have the luxury of being able to decide whether auditors can or should specialise in certain types of work; many smaller units will simply not have that choice and will have to train all their QA staff to be capable of auditing all study types on offer. Even some larger CROs may elect for this comprehensive training approach in the quest for ultimate flexibility, broader vision and to enable a more personal service to their Sponsors. There is no right or wrong way and, again, effectiveness is the key.

### 19.5.1 Study Plans

The GLPs mandate that the Study Plan or Protocol is inspected, and every CRO running complete GLP studies will do this. What varies is when this is done; either as a late draft or immediately after authorised issue and usually well after any detailed Sponsor input to the design of a study. Here the



GLPs do not specify but it is very unlikely that a CRO will audit the same study plan at both timepoints in the simple interests of efficiency. The majority of study plans will be based on established templates that have been completed and then tailored to a particular Sponsor's requirements, and so the QA inspection of study plans is commonly a routine exercise. Any amendments to the Study Plan will also be audited and here the issue for CROs is timeliness of issue – study plan amendments define planned changes to a study and so it is important that any Sponsor input or approval is performed promptly if their actions are not to delay issue of the amendment to a point where it becomes retrospective.

The planning of study-specific inspections will occur at this stage and so it is important for a Sponsor to understand that any additional requirements should be explicitly communicated and preferably specified in the Study Plan itself. Inspection requirements over and above the CRO's own standard procedures can usually be accommodated, though of course the CRO will object if they feel that over-inspection or unnecessarily intensive audit is drawing them towards an uncomfortable QC position. In any event, additional QA input is likely to be outside the costed scope of any work and may attract additional charges, particularly on smaller studies.

### 19.5.2 Inspections

GLP mandates three types of inspection but really gives no further useful guidance in the regulations themselves. Study-based, facility-based and process-based inspection activities should all be defined in SOPs and should occupy a significant proportion of the total QA resource if the programme is not to slide down the slippery slope towards QC. While there are no hard and fast rules, QA managers should be aiming to occupy about half of their resource with inspection activities – as opposed to data and report auditing activities – in order to maintain an appropriate balance of 'in-life' activities. In practice, this balance needs to be somewhat flexible to ensure that transient work peaks are managed sensibly but the overall trend needs to be kept in view. The historic reason behind this is quite simple: spend too great a proportion of available time on the report audit process and the QA programme will surely decline into a checking service seen as an integral part of the report production process – and that was never the intention of defining an independent QA function.

A distinguishing feature of many CROs is the volume of work they undertake. High throughput volumes often mean that procedures that may be relatively rare in many facilities become routine and repetitive in a busy CRO. The frequent and standard nature of these processes lends them to a random sample – or process-based – inspection approach rather than a study-specific approach. Indeed, the QA programme may include a greater proportion of process-based inspections than study-based inspections though this scenario will be confined to the very largest CROs and those performing a very narrow range of processes such as dedicated histopathology laboratories. For most, the QA inspection programme will comprise a balance of study-based inspections where one or more specific visits are made to a particular study and a background programme of process-based inspections covering routine and repetitive supporting procedures. The key is to ensure that critical phases are inspected at adequate intervals on the study-based programme and that procedures selected for the process-based programme truly are routine, repetitive and representative of the pool of studies they are intended to reflect. It is not uncommon for Sponsors and Regulators to seek assurance that a process-based inspection programme is well designed, robust and defensible in relation to the current volume and variety of throughput. In fact, process-based inspection programmes probably attract more attention from regulatory inspectors than any other QA activity.

Quality Assurance must maintain an awareness of current study loadings by regular reference to the GLP Master Schedule and be prepared to adjust the process-based inspection programme accordingly; being unable to fulfil a planned inspection programme because the target procedures



are simply not happening is unacceptable. The programme should be proactively managed and procedures that decline in availability should be transferred back to study-specific inspection. Similarly, novel or uncommon procedures are often developed or taken on by CROs and these should be inspected on a study basis at least until they become standardised and their frequency increases to the point where transfer to the process-based programme becomes defensible. Overall, the CRO should be able to present their process-based programme in the context of the proportion of representative studies or process inspected to demonstrate that coverage is consistent, representative and unbiased.

Inspection frequency is not defined in calendar terms in the GLPs. The key is to maintain a frequency which ensures QA visits to a Study or Facility are not so regular and predictable as to become an expected part of every technical process. Too frequent inspections erode independence by allowing the QA presence to become involved – anyone who turns up too often or stays too long inevitably gets given something to hold or a job to do! Common intervals in the industry include a three- or four-month cycle for process-based inspections and a similar frequency for repeated study-based inspection; longer intervals could be considered inadequate to assure the integrity of studies and are likely to be challenged at regulatory inspection. Although there may be slightly more scope to extend time intervals in a facility-based programme, common frequencies here lie in the range of 6–12 months.

Missed inspections should be a rarity and should always be well documented. Regulators will look for adequate planning and communication as well as adequate QA resource, so the reasons for missing any inspection should be logged and addressed. Some short studies present only a single inspection opportunity and to miss that jeopardises the whole study; in fact, any type of regulatory study can be declared out of compliance if QA inspection coverage does not meet regulatory expectations or is entirely absent.

Particularly in larger CROs, the volume of work conducted can mean that the inspection programme requires significant planning and co-ordination in order to maximise efficiency. With multiple studies being conducted in the same timeframe, it is easy to see the risk of despatching three or four auditors into the same facility at once to inspect a single process each in parallel, when a little planning and flexibility means that one person could inspect all events in series. Volume also means that there will be many inspections to report, track, follow-up, analyse and archive and so again the larger CROs will tend to have dedicated resource for this endless task. Increasingly the trend is towards electronic reporting of findings, with on-line tracking and responses eliminating much of the effort needed in manual systems. However, the inspection reports themselves are handled, there will probably always be the need for the human touch in precise planning to ensure QA arrive at the right place, at the right time and in the most efficient manner.

### 19.5.3 Report Audits

Sponsors have the right to expect a quality product from a CRO and the final study report will carry the torch for that organisation. The report is the final product and will be seen by many individuals. Each of them will form an opinion based on what they see and so CROs will expend considerable effort on the science as well as on the presentation in order to preserve their reputation.

Audit of the draft final report in a Contract environment should, in principle, be as routine as auditing study plans. Both are constructed around templates to a relatively standard format. These days, much of the bulk of detail in reports lands on the page by electronic means from direct capture systems or ‘data warehouse’ databases with little or no human intervention. Only the textual sections of reports – the material, methods, results, discussion and conclusion – are likely to have experienced significant manual input. There are, however, a number of issues around report production in Contract organisations that make this audit process somewhat strained at times. The

most prevalent issue is one of time pressure – contractual delivery points mean that precise scheduling throughout is key and thus even slight slippage at any point may mean that the time allocated for QA review of the report is squeezed. Most CROs will have compiled statistics on audit times across the range of study types on offer, as an integral part of the business development and quotation process, to allow the generation of appropriate costing and reasonable timings. Audit, of course, is neither an exact science nor a mechanical process and so there will always be variation in the amount of resource used to perform an effective audit. High quality, error-free drafts will be audited much more quickly than a draft report containing errors and inconsistencies; good reports have fewer corrections to be made after the QA audit and so can be issued much faster than one requiring many edits. A draft report compiled in a hurry is likely to contain a higher error rate than one composed with due focus and care. If there was ever a place for the old adage “more haste, less speed” this is it. The odds on a report constructed in haste and arriving late for audit into QA containing more than the average error rate are very short indeed. The pressure on QA to burn the midnight oil in attempt to audit such a late report and still meet the deadline for issue can be immense – and the risk of QA collapsing into a QC role now reaches its greatest height.

These pressures mean that QA has to be particularly robust during the audit process, and may even be so brutal as to decline any action at all unless evidence of appropriate QC input is forthcoming. More commonly, QA will have agreed an Acceptable Quality Level with Management and apply a range of sampling methods at audit to demonstrate in the shortest possible time that a report is fit for its intended purpose. Thankfully, QA also holds the master trump card at this time – the signed QA statement is an essential component of any GLP report and without it that report has every possibility of intense regulatory scrutiny or rejection. The slightest threat of withholding signature on that statement until corrections are made and outstanding actions completed is usually enough.

While the Study Director retains overall responsibility for the conduct and reporting of a GLP study performed at a CRO, the Sponsor will almost inevitably provide comments and suggestions on the content of the report for that study. Handling that input lies with the Study Director, but QA will need to review related changes to assure that compliance and accuracy is maintained – and on occasion this can mean re-audit of significant sections. Increasingly, the CRO world is expected to produce reports in formats defined by the Sponsor, rather than their own. Although this is usually straightforward, it is of course one more thing for someone to monitor and that task may also fall to QA.

## 19.6 ROLE OF QA IN MULTI-SITE STUDIES

Multi-site studies in CROs are probably now the norm rather than the exception, particularly when it comes to toxicology portfolios. Sponsors will commonly retain phases of studies involving analysis of samples, often because they already have the validated method; some will peer-review histopathological evaluations to ensure consistency across studies while others will insist on using the services of a third party for defined phases. Whenever a multi-site study arises, a CRO's QA has to adopt a proactive communication style to engage with QA at the other test sites involved. This communication begins at the planning stage, and continues throughout the study up to the point of archiving. Just as with inspections, these communication channels generate a volume of issues to track and follow up and can take a significant amount of resource to handle properly. Most external input to multi-site studies will come from facilities which are themselves GLP compliant, and so the ‘Lead’ QA audit requirements are usually minimal – just a quick review for completeness and fit.

However, when external input comes from facilities – including those of the Sponsor – which are not ‘certified’ GLP facilities, ‘Lead’ QA audit requirements escalate. If compliance is to be claimed for such delegated phases, the performance of that phase should be monitored (on site) by ‘Lead’ QA and by the Study Director to the satisfaction of the National GLP Monitoring Authority. Raw data contributions will also need review and the CRO's QA can often encounter difficulties in trying to audit against remote SOPs. Clearly, this is a scenario best avoided but there is a real

‘Catch 22’ situation when the Sponsor insists on such a facility. QA’s reserves of pragmatism, tact and diplomacy can be stretched to the limit. Effective planning and communication are everything.

## 19.7 RELATIONSHIP OF QA WITH MANAGEMENT, STAFF AND SPONSORS

The way QA conducts itself in Contract is really no different from any other GLP environment. The very nature of the job means that auditors have to work constantly to maintain a professional and constructive footing with Study Directors, technical staff and Management alike. Strong interpersonal skills are key. The unique aspect is that QA is very *visible* in Contract. QA’s policies, procedures and behaviours are constantly on display to Sponsors, whether evident in communications or seen first hand during visits QA really does exist for all to see. Even though few Sponsors will ask to see the CRO’s own detailed QA comments on their studies, most will gauge their effectiveness and form an opinion about QA’s ability positively to influence compliance standards. Some Sponsors rely on the CRO’s QA so heavily that they never send an auditor of their own, while others will simply visit occasionally during a programme of work and work with QA to ensure no misunderstandings occur. Whichever approach to monitoring they chose to take, there is no doubt that Sponsors expect a CRO’s QA to be very effective and driving a very high level of quality and compliance on their studies – yet they also expect that same QA function to be ultimately understanding and forgiving. As has been said before, flexibility and pragmatism are essential traits. The rewards come in the very occasional piece of feedback from a Sponsor which indicates that the CRO’s QA function was the deciding factor in the placement of outsourced studies.

## 19.8 QA ADDING VALUE

In Contract, QA simply has to add value. Going through the motions of the minimum QA processes required by the GLP regulations will not set your CRO apart from the competition. Paying cursory attention to compliance requirements, relying on a blinkered checklist approach to every inspection and just ‘kicking the tyres’ at facility evaluations will not work for long. Paradoxically, QA is expected to drive compliance standards yet remain demonstrably independent. Although care must be taken to guard against encroaching dogma, QA will often be used as a major source of regulatory advice and guidance – particularly when errors occur.

Sponsors and regulators expect the QA function to have a broad understanding of every aspect of the facility, even in the largest CROs. Representing the whole CRO by hosting Sponsor visits, particularly where compliance monitoring is on the agenda, is commonplace. An active involvement in corrective and preventative action programmes is the norm, and significant input into regulatory training initiatives is almost universal for QA.

Sponsors and GLP Monitoring Authorities expect CROs to be at the forefront of compliance standards, so networking amongst industry colleagues is particularly important to keep abreast of current issues and trends. The ability of a CRO’s QA management to assimilate, digest and communicate breaking news of novel regulatory stances can be instrumental in protecting ongoing studies against future criticism. Other value-adding activities which QA is well-placed to facilitate or contribute to include process improvement programmes, customer complaint handling, risk-based assessment of compliance issues, industry benchmarking and – of course – hosting Regulatory Inspections.

## 19.9 CONCLUSIONS

The constant multi-faceted input to a CRO’s compliance and audit systems mean that they are often highly evolved and robustly built, yet tend to be flexible and efficient. The pressures of volume, variety and time mean that Contract is a fascinating environment in which to develop QA philosophies under intense scrutiny. Overall, Contract Research is a very complex industry balancing science, compliance and customer service with QA at the centre.

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# Good Laboratory Practice and Pharmacology

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## 20.1 INTRODUCTION

The types of study designed to investigate the pharmacology of a test substance are varied and depend, to a certain extent, on the properties of a compound. Safety pharmacology studies should be designed to investigate the effects of a pharmaceutical substance and also to investigate any side-effects of the substance.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S7A is the internationally accepted reference guideline describing the requirements of pre-clinical safety pharmacology for human pharmaceuticals. This text requires that pharmacology studies that aim to define the dose–response relationship of a pharmaceutical compound’s effects on the three major vital organ systems of the body (namely the central nervous system, the respiratory system and cardiac function) be conducted to GLP. It also requires that follow-up studies providing a greater understanding of the potential for pharmacodynamic effects should be conducted to the greatest extent possible to GLP.

The ICH S7B guideline further refines the cardiovascular requirements, specifically with respect to delayed ventricular repolarisation (*i.e.* QT prolongation). There are European regulatory initiatives recommending drug dependency or drug withdrawal studies to be conducted to GLP.

It is recognised that, for practical considerations, it may not be feasible to conduct some safety pharmacology studies to GLP.

Safety pharmacology studies are generally not performed on veterinary drugs, industrial or agricultural chemicals.

## 20.2 DEFINITION OF SAFETY PHARMACOLOGY

Pharmacology studies fall into three categories:

- “*Safety pharmacology* studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.”<sup>1</sup> Historically, terms such as general pharmacology, ancillary pharmacology, secondary pharmacology, high-dose pharmacology and regulatory pharmacology have also been used to describe the field. Nowadays, safety pharmacology is considered a discipline in its own right.
- *Primary pharmacology* studies are designed to investigate the *desired* pharmacological property of a compound, *e.g.* effects on blood pressure for a hypertensive agent.

- *General pharmacology* and *Secondary pharmacology* studies are the same. These studies are designed to investigate *untoward* actions of a compound, which maybe related to the compound's mode of action that is outwith its intended clinical use. An example would be the respiratory depression caused by opiate analgesics.

### 20.3 HISTORY OF GOOD LABORATORY PRACTICE FOR SAFETY PHARMACOLOGY STUDIES

Since its inception, Good Laboratory Practice (GLP) has been applied to non-clinical safety studies in many areas of chemical and pharmaceutical testing. For pharmaceuticals, prior to the early 1990s, this applicability of GLP was inferred to be pertinent to toxicology studies only, and not to pharmacology or pharmacodynamic studies. However, since then, the notion of a grey area (Figure 1) has developed, where certain pharmacology studies overlap with the determination of the *safety* of a pharmaceutical test substance.

During the early 1990s, the applicability of GLP to pharmacology studies remained an issue amongst testing facilities conducting non-clinical laboratory studies, each laboratory adopting its own stance in the absence of any clear guidelines.

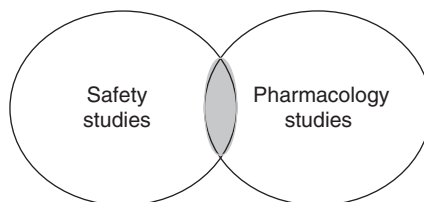
The European directive 91/507/EEC (part 3 of the Annexe)<sup>2</sup> requires GLP to be applied to “pharmacodynamic studies designed to test the potential for adverse effects”. However, there was no such requirement in the American Food and Drug Administration (FDA) legislation at that time; neither was there any clear guidance from any regulatory body as to what study types constituted pharmacodynamic or pharmacology studies.

In 1995, the Japanese Ministry of Health & Welfare issued a first detailed definition<sup>3</sup> of the safety pharmacology studies required for registration of a pharmaceutical new chemical entity (NCE). In the absence of any other legislation, the comprehensive list of study types described therein was adopted by many laboratories.

A study in 1995 by Sullivan and Kinter<sup>4</sup> demonstrated that 62% of pharmaceutical companies surveyed undertook pharmacology studies to GLP standards. Kinter and Dixon<sup>5</sup> noted that implementing GLP compliance for safety pharmacology studies increased the cost of these studies by 10–20%.

In 1996, the European Medicines Agency Committee for Propriety Medicinal Products (CPMP) drafted a document entitled “points to consider”<sup>6</sup> on QT prolongation, which recommended routine *in vitro* screening of all non-cardiac drugs.

In the ICH non-clinical safety guidelines, the term “safety pharmacology” first appeared in the topics M3 (“Timing of non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals”)<sup>7</sup> and S6 (“Preclinical safety evaluation of biotechnology derived pharmaceuticals”),<sup>8</sup> but it was not until 11 March 1999 that a document entitled “Draft guidelines for *safety pharmacology* studies (version #0.5)” was produced. This was the basis of ICH S7A (*ibid.*). When ICH S7A came into operation in June 2001, it introduced much needed clearness to the field of regulatory pharmacology.



**Figure 1** Studies to determine a test substances' effect overlap with those studies intended to determine its' safety



Currently, GLP applies to a core battery of pharmacology studies, and should also be applied (in the words of ICH S7A) “to the greatest extent feasible” to other follow-up pharmacology studies.

## 20.4 SAFETY PHARMACOLOGY STUDY TYPES

It is impossible for regulators to give in detail the recommended methods for either the core battery of safety pharmacology studies or any follow-up studies, partly because the study design may well depend on the type of compound (especially for follow-up studies) as pharmacological effects vary markedly depending on the class of compound tested, and also partly because the choice of methods is continually evolving. Study design is a topic of much heated discussion as no uniform consensus has been reached within the industry. Hence, different laboratories use different choices of study types, differing methods and even different test systems, several of which present technical or scientific challenges. However, safety pharmacology studies show a good predictive potential for humans, although it is recognised that there are species differences.

The ICH S7A (*ibid.*) requires that the core battery of safety pharmacology tests investigates the three most vital body functions, *i.e.* central nervous system, respiratory system and cardiovascular function with *in vivo*, *ex vivo* or *in silico* studies.

### 20.4.1 Cardiovascular Studies

These may be chosen from the following:

- Cardiovascular studies to cover blood pressure, ECG, and vascular effects and extended telemetry studies.
- Human ether-a-go-go-related gene (*hERG*) cardiac potassium channel studies – determining potassium ion channel current blockade that predicts potential arrhythmia hazard.
- Isolated cardiac tissues such as Purkinje fibres, papillary muscles or trabeculae – determining cardiac action potential duration and indicative of potential QT prolongation. These types of studies are now becoming of low priority in many laboratories.

### 20.4.2 Respiratory Studies

These may be chosen from the following:

- Whole body plethysmography
- Head-out plethysmography
- Blood gas (*e.g.* O<sub>2</sub> and CO<sub>2</sub>) concentrations (sometimes using anaesthetised animals)
- Airway resistance
- Isolated trachea.

### 20.4.3 Studies into the Central Nervous Systems (CNS)

These are invariably carried out using *in vivo* models. This is because the neurological responses are less well understood and less well modelled than those of the organ systems.<sup>9</sup> Their endpoints are also among the most difficult responses to interpret, especially for studies of lethargy, visual acuity or motivational assays, especially if these studies are conducted outside the home cage to which the animals are accustomed. CNS studies may include a selection from the following:

- Gross behavioural observations
- Functional observation battery (FOB) of tests
- Locomotor studies, *e.g.* activity wheels, open field, photocell activity cages



- Motor coordination, *e.g.* rota-rod or beam walking
- Analgesia
- Sleep induction
- Righting reflex
- Memory tests, *e.g.* passive avoidance, active avoidance, mazes
- Learned behaviour.

Depending upon the mode of action of a substance, subsequent pharmacology studies may include the following:

- Renal system, *e.g.* diuresis, blood chemistry, *etc.*
- Studies into the autonomic nervous response of smooth muscle tissue
- Effects on the digestive system, *e.g.* gastric ulcer formation, intestinal transit-times, ileum contractility.

#### 20.4.4 Abuse Potential Studies

The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) issued a “Guideline on the non-clinical investigation of the dependence potential of medicinal products” (April 2005).<sup>16</sup> This position paper recommended that “first tier” or early development screening studies “generally do not need to meet the requirements of GLP, although scientifically high standards should also be maintained”. It recommended that all CNS-active medicinal compounds be further tested for potential to cause dependence (either a withdrawal syndrome or by presenting reinforcing properties), and recommended that this “second tier” of studies, *i.e.* specific behavioural animal models be conducted in compliance to GLP, to the greatest extent possible.

While there is enthusiasm for conducting these studies to high scientific standards, there is little industry buy-in to this GLP requirement, as most expertise and knowledge in the domain is currently placed within university centres that generally do not comply with current GLP requirements.

Although the above list is by no means exhaustive, a laboratory will not conduct all these studies. More details of pharmacology study design and methodology can be found in publications by Pugsley<sup>10</sup> and Wakefield *et al.*<sup>11</sup>

Currently much work is ongoing to try to reduce, refine and replace many *in vivo* studies with alternatives.

It is also important to recognise the importance of feeding or fasting that will change the systemic exposure and hence the pharmacological effects of a drug. There is often a sex difference in pharmacological response. Studies tend to be performed on male animals as the first dosing in humans is customarily in men not women.

### 20.5 DIFFERENCES BETWEEN SAFETY PHARMACOLOGY STUDIES AND TOXICOLOGY STUDIES

Safety pharmacology studies are of fundamental importance in elucidating the mechanisms by which a medicinal product produces its therapeutic effects. Additionally, pharmacology studies may also contribute to the understanding of toxicological phenomena.

Safety pharmacology studies are generally performed with single-dose (sometimes escalating) administration. As studies are designed to investigate pharmacological endpoints, rather than toxicological tissue damage, necropsies are rarely performed. Hence, after a suitable washout

period, animals may be reused in a subsequent study (assuming that the pharmacological effects have not been too pronounced). This is especially true for large or instrumented animals. A proportion of safety pharmacology studies routinely use positive as well as negative controls.

Pharmacology studies are often run at an early stage of the development of a compound when the test substance has not been fully characterised. Any lack of characterisation of the test item or its subsequent formulation should be clarified in the Study Director's compliance claim in the final study report.

Supplementary pharmacology studies may be required to elucidate findings that have arisen in clinical studies; hence a fast response is required, even if a new experimental model has to be devised.

## 20.6 TEST SUBSTANCE DOSE LEVELS

Safety pharmacology studies should establish the dose–response relationship of the effect observed. As pharmacology studies' investigations should be made over the post-dosing time period in which the drug is pharmacologically active, it is important to have pharmacokinetic data available – collected contemporaneously to the study or under similar conditions. These data also help to determine quantitative exposure to the drug or to its metabolites.<sup>12</sup> Dose levels of pharmacology studies may well be typically lower than those of toxicology studies.

## 20.7 TIMING OF SAFETY PHARMACOLOGY STUDIES

The core battery of tests on the cardiac, CNS and respiratory functions should be undertaken prior to the first compound administration in humans. Other organ systems, *e.g.* renal or gastrointestinal systems, are less important as their malfunction is not immediately life threatening, and hence safety pharmacology of a drug on these systems can be investigated in supplemental pharmacology studies. These follow-up studies should be conducted in parallel to the appropriate stages of the clinical development of a pharmaceutical drug substance (unless this organ system is itself the target organ or tissue system of the drug).

## 20.8 APPLICABLE GUIDELINES

The tripartite consensus document ICH S7A entitled “Note for guidance on Safety Pharmaceutical Studies for Human Pharmaceuticals” and ICH S7B<sup>13</sup> entitled “Guideline on Safety Pharmacology Studies for assessing the Potential for Delayed Ventricular Repolarisation (QT interval prolongation) by Human Pharmaceuticals” provide internationally accepted definitions and objectives for safety pharmacology studies.

This first document recommends that the *in vivo* and the *in vitro* investigations into the effects of the test substance on certain vital functions (the central nervous system, the cardiovascular system and the respiratory system) be performed to GLP.

Follow-up and supplemental pharmacology “studies should be conducted in compliance with GLP to the greatest extent possible” (ref. ICH S7A *ibid.*). Primary pharmacodynamic studies do not need to be conducted to GLP. Secondary pharmacology studies do not routinely need to be conducted to GLP, unless their results play a key role in the safety evaluation of a substance.

The safety pharmacology studies referred to in the ICH guidelines should be used to provide early information for risk assessment, to determine a therapeutic window for clinical dosing and to give details about anticipated side effects in early clinical trials.<sup>14</sup>

A few pharmaceutical companies chose to perform some studies (*e.g.* *hERG*) to an internal quality standard that assures study integrity and data reliability, rather than performing them to GLP. Some regulatory bodies have raised questions about this practice.<sup>15</sup>

## 20.9 FUTURE TRENDS IN SAFETY PHARMACOLOGY STUDIES

### 20.9.1 Translational Pharmacology

The concordance with human pharmacology of results for *in vitro* and *in silico* studies is continually being improved; pharmacodynamic biomarkers will have an increasing role to play in this field. These may be coupled with pharmacokinetic/pharmacodynamic research into the duration of action of test items. The safety pharmacology of major metabolites is increasingly being studied too.

### 20.9.2 Juvenile Animals

Some laboratories are starting to investigate safety pharmacology profiles in juvenile animals as a predictor of effects in subsequent paediatric clinical trials.

### 20.9.3 Central Nervous System Studies

As models improve, more types of studies may be included in the core battery of tests, *e.g.* study of suicidal tendency for anti-depressive drugs.

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## CHAPTER 21

# Application of GLP in Analytical Chemistry with Cross Reference to GMP and GCP

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### 21.1 INTRODUCTION AND SCOPE

The scope of this chapter is to discuss the regulatory issues involved in analytical chemistry. It is not intended to discuss in detail the technical aspects of a wide range of analytical techniques, although where the “how to” implementation of regulations is made clearer by reference to the technical issues this will be done.

In a non-clinical environment good laboratory practice (GLP) is the definitive practice applied in analytical laboratories. However, the application of GLP is more complex where some of these laboratories support clinical or good manufacturing practice (GMP) for manufacturing activities. The following types of analytical laboratories are discussed further in this chapter.

Analytical laboratories, which analyse the formulation of diets and dosing formulations for GLP-toxicology studies, are defined as formulation analysis.

Bioanalytical laboratories are those laboratories which analyse biological fluids in man or animals for the purposes of defining/understanding the kinetics of the test article under investigation. Evaluating the impact of the test article on the biochemistry of man or animals is carried out in clinical chemistry laboratories, sometimes known as chemical pathology (see also Chapter 11).

Last but not the least, those laboratories which analyse pharmaceutical formulations, which are designated to be used by man either during the development phase or of the final marketed product, are defined as pharmaceutical analysis.

Thus the areas to be reviewed are formulation analysis, bioanalysis, clinical chemistry and pharmaceutical analysis.

In the past few years a draft guidance for analytical chemists was developed by the UK industry representatives and the MCA. The document was primarily intended to guide formulation chemistry analysts, largely involved in the analysis of toxicology formulations.

Although discussions at the time suggested it may have generic application in a GLP environment, this document was not finalised as such, and has been modified by one of the original authors (A. Anderson) to form the basis of this chapter.

### 21.2 ANALYTICAL CHEMISTRY IN A GLP LABORATORY

GLP is concerned with the organisational processes and conditions under which studies are planned, performed, monitored, recorded and reported, in order to promote and maintain the quality and reliability of test data. Testing facility management has the ultimate responsibility

for ensuring that the facility is effectively organised and that work is carried out to a high standard, in accordance with GLP and relevant national legislation concerning the health and safety of all staff.

### 21.2.1 Management

Management must establish procedures for the appointment of a study director or principal investigator as may be appropriate.

When a principal investigator has been appointed to direct a phase of the study on behalf of the study director, documented procedures should exist to describe the responsibilities of both the study director and principal investigator. Both parties should be aware of any findings resulting from quality assurance (QA) audit activities.

Where it is appropriate for management to give specific responsibilities for defined activities to designated persons, these responsibilities should be defined in their job descriptions and, when necessary, they should have received relevant training. Such responsibilities might include receipt and care of test and reference materials, calibration and maintenance of equipment.

### 21.2.2 Quality Assurance

Many of the studies and procedures undertaken in the analytical laboratory are of short duration, frequently undertaken and routine in nature. It may, therefore, be appropriate for QA monitoring to be process-based, and the inspection programme must cover each study type or activity (Chapter 17). The frequency of such inspections should be specified in QA standard operating procedures (SOPs), which take into account the numbers, frequency and/or complexity of procedures being conducted in the laboratory.

The work undertaken by the analytical laboratory may be part of a multi-site study. In this situation the responsibilities of the QA units at each site must be clearly defined.

Where a part of the study has been conducted at a different facility a statement should be prepared by the QA unit of that facility, clearly identifying the study activities to which it refers.

The study director and principal investigator(s) should receive reports of all relevant QA activities and findings. Where required a formal QA statement may be prepared.

### 21.2.3 Facilities

The size, design, construction and location of the analytical laboratory should be suitable for the type and volume of work being undertaken. It is recommended that there should be sufficient space to allow effective separation of the various activities, *e.g.* separate areas for the 'wet chemistry' and instrumentation. It may be appropriate for specified areas of the laboratory to be set aside for the receipt and storage of samples and test/reference items. There should be sufficient space allowed to accommodate the samples, reagents and paperwork associated with the use of laboratory apparatus. It may be necessary to provide special storage facilities, *e.g.* refrigerators, freezers.

Most importantly, consideration needs to be given to the prevention of sample cross-contamination and the contamination of samples with test/reference items. Where there is a risk of cross-contamination there may be a need for physical separation of common activities. This may necessitate the use of a separate laboratory or working area, *e.g.* fume cupboard. Where physical separation of activities is not possible they should be separated in time, especially use/reuse of glassware.

In all areas, the levels of cleanliness and housekeeping should be of the highest order. It may be advisable to dedicate certain items of apparatus/instrumentation for specific functions, *e.g.* for the



handling of control samples. Within the analytical laboratory regular and correct disposal of waste is of importance both from the study and safety perspective.

#### 21.2.4 Instrumentation, Materials and Reagents

Adequate equipment should be available for the proper conduct of studies. It should be suitable for its intended use and be properly qualified, calibrated and maintained to ensure accurate performance. The organisation of laboratory areas and activities should be such as to accommodate the apparatus, bearing in mind the need for adequate space for sample handling and associated documentation, *e.g.* study plans, standard operating procedures, sample tracking records.

Instrumentation, usually involved in some aspect of the quantitation is differentiated from equipment, *e.g.* shakers.

##### 21.2.4.1 Equipment

**21.2.4.1.1 Qualification.** Before being used for regulatory work equipment should be tested to ensure that it operates satisfactorily. For critical items of equipment a more formal validation may be required. This is particularly important for computerised systems, which capture, manipulate or store data (Chapter 37).

Any significant changes or modifications subsequently made to the equipment should be documented and the need for revalidation considered. Some modifications to equipment such as change of columns in gas/liquid chromatographs are part of the normal usage of the apparatus and are normally assessed during calibration, using system suitability criteria (SSTs). Modifications such as software upgrades for computerised systems are usually regarded as major changes and should go through a formal change control and re-validation process.

**21.2.4.1.2 Calibration.** Where appropriate, test and measuring equipment should be calibrated to ensure the values obtained are correct; calibration standards should be traceable to national/international standards. Where these do not exist the reference standard used should be specified. The integrity of all calibration standards should be preserved.

Calibration frequency, method and tolerance/acceptance criteria should be documented. The need for re-calibration should be considered following any events, *e.g.* moving location, damage/repair that may affect the validity of the previous calibration.

Records of calibration (whether performed in-house or under contract) should be established, maintained and be available for inspection.

In the event of a piece of equipment being found to be operating outside its acceptance criteria, documented procedures should state what actions are required. Each such event should be critically assessed to determine whether the integrity of any previously generated data or measurements is compromised. All decisions regarding the integrity of such data or measurements should be recorded.

**21.2.4.1.3 Maintenance.** Documented maintenance procedures, covering both preventative maintenance (where applicable) and work resulting from faults or breakdown, should be established. It might be appropriate to appoint a designated person to be responsible for the co-ordination and management of maintenance/calibration activities.

Maintenance logs and calibration records that provide the supporting information necessary to verify the validity of raw data or to permit reconstruction of a process should be retained in the archives (Chapter 36).

**21.2.4.1.4 Routine Use.** Documented procedures that describe how to use the equipment should be available. Supplier instruction manuals can be used for reference purposes where appropriate (*e.g.* set-up, fault finding). If used, these become subject to normal document-control procedures and must be retained as historical records when the equipment is no longer used.

Study records should identify which critical items of equipment have been used to generate raw data.

**21.2.4.2 Materials and Reagents.** Materials and reagents whether purchased or prepared in the analytical laboratory should be of suitable quality for their intended use. The in-house preparation of materials and reagents should be fully documented. A policy for the allocation and review of expiry dates should be established. The expiry date should be based on the known physical and chemical properties of the material or reagent and its intended use. In certain circumstances, *e.g.* with very stable materials or reagents, it may be appropriate to assign a period of use rather than a definitive expiry date.

For materials and reagents received in sealed containers it might be appropriate for the expiry date or period of use to be assigned from the date of opening.

When materials and reagents have been assigned a long period of use, the possibility of inadvertent contamination during repeated laboratory handling should be taken into consideration.

All materials and reagents should be labelled with the following as appropriate:

- description and/or identification, including grade and concentration where appropriate;
- date of preparation (not required for purchased chemicals/reagents);
- identity of person making preparation (not required for purchased chemicals/reagents);
- expiry date or period of use;
- storage conditions.

Materials or reagents should not be used beyond their expiry date. At such a time, they should be discarded in accordance with documented procedures.

However, in some situations, it may be acceptable to extend the working life of a material or reagent by demonstrating that it remains fit for use. This may include an assessment of stability/purity characteristics. In this situation the supporting data should be retained, possibly including the preparation of a new certificate of analysis and the new expiry date or period of use recorded.

## 21.2.5 Standard Operating Procedures

Each laboratory area should have, immediately available, copies of the standard operating procedures relevant to the activities carried out in that area (Chapter 16). Other sources of information, such as analytical methods, textbooks, published references, *etc.* may be used as supplements to these procedures. Where this is the case, full reference to the source should be included in the raw data.

The following are illustrative examples of standard operating procedures relating to laboratory activities.

**21.2.5.1 Test and Reference Items.** Receipt and handling, labelling and traceability, identification, characterisation, storage, measures to prevent cross contamination.

**21.2.5.2 Equipment, Materials and Reagents**

**Apparatus.** Use, maintenance, cleaning, validation, calibration and/or standardisation, environmental monitoring of storage facilities.

**Computerised systems.** Validation, operation, maintenance, security, change control and back-up.

**Materials and reagents.** Preparation and labelling.

#### 21.2.5.3 Laboratory Operations.

- Sample handling: Receipt, preparation, taking a homogeneous sample, storage
- Housekeeping and waste disposal, control of methods of analysis
- Validation of the analytical procedure, method acceptance criteria

21.2.5.4 *Documentation.* Control and handling of documentation, definition of raw data, data collection, preparation of the analytical report or final report, storage and retrieval.

### 21.2.6 Study Plan

21.2.6.1 *General Requirements.* For each study there should be a written study plan which clearly describes the objectives of the work and the methods to be employed (Chapter 15).

If the work of the analytical laboratory constitutes one part of a study, the laboratory should still receive the complete study plan and all subsequent amendments.

The study plan should fully describe all analyses that will be carried out; there should be information on the samples to be tested, the tests required and details of the analytical methods to be employed. This information might be provided by reference to standard operating procedures or other published information.

There might be occasions on which precise details of the analytical work required, *e.g.* number and type of samples are not known at the time when the study plan is approved. As soon as details are known they should be documented in a study plan amendment before commencing any analytical procedures. In certain situations where the analytical work is the responsibility of a principal investigator it may be appropriate for the principal investigator to determine and approve the analytical methodology to be used. Details of the methodology used must be recorded in the study file.

21.2.6.2 *Generic Study Plans.* For studies that are wholly analytical in nature it might be possible for the study plan to be simplified. However, the essential information required by the principles of GLP must still be provided in an unambiguous form.

Where a particular type of study or series of such studies are performed frequently within a laboratory, it may be appropriate to prepare a generic study plan, which contains the majority of information applicable to such studies. When a single generic plan containing information for short-term studies performed frequently within a laboratory is used, approval signatures must be obtained from the testing facility management, the Study Directors responsible for the conduct of these studies and QA.

The study-specific supplement with details of sponsor, test material, *etc.* should then be issued as a supplementary document requiring the dated signature of the designated study director. The combined document – the generic study plan and the supplement – is the study plan.

It is important that all such supplements are provided promptly to the test facility management and QA.

### 21.2.7 Laboratory Procedures

Where a laboratory undertakes both regulatory (GLP) and non-regulatory work it is essential that the conduct of the non-regulatory work does not compromise the GLP compliance status of the

laboratory or of the regulatory work. To ensure that GLP compliance is maintained all work within such laboratories should be conducted in accordance with the principles of GLP.

*21.2.7.1 Receipt and Log-In.* Procedures should be in place for recording the receipt of samples/test and reference materials and for providing each with a unique identification.

If sample identification is by means of an adhesive label, it should be placed in such a way as not to obscure the information on labels already attached to the container.

Upon receipt, the condition of all samples/test and reference items should be inspected as soon as practical and verified as acceptable in accordance with the relevant study plan or standard operating procedure. Any deviations should be documented and brought to the attention of the study director or management, as appropriate.

Any laboratory samples (sub-samples) subsequently produced should be labelled so as to maintain traceability throughout their lifetime in the analytical facility.

For test and reference items the following data should be recorded as appropriate:

- Date of receipt
- Source of supply
- Identity/batch reference
- Certificate reference (where available)
- Purity
- Amount received
- Expiry date or period of use as appropriate
- Storage conditions

Analytical standards or stock solutions, prepared from test/reference items, must be labelled such that the test or reference item used for their preparation can be identified. Any derived working solutions should be similarly labelled to provide a complete audit trail.

*21.2.7.2 Storage.* Correct storage of samples or test and reference items in the laboratory is of primary importance.

Specified areas of the laboratory should be set aside for the receipt and storage of samples, test and reference items.

All storage locations should be secure and where special environmental conditions exist the facilities should be monitored to ensure that the designated storage conditions are maintained.

The acceptable ranges for any specified environmental conditions (*e.g.* temperature/humidity) should be defined in appropriate documentation.

If storage conditions have exceeded the defined limits the possible effects on the acceptability/integrity of any samples or test and reference items should be considered. If it is considered that the samples/items have not been adversely affected this decision should be recorded in the raw data.

Special care is required for all test and reference items as they may affect the integrity of associated analyses. These items should be stored under specified conditions and should preferably be kept separate from associated samples for analysis. All samples, test and reference items should be stored in appropriate containers.

*21.2.7.3 Traceability.* All samples and test/reference items received in the laboratory should be allocated to appropriate storage areas and the storage location recorded. A chain of custody must be maintained from receipt until disposal.

After analysis, samples/items may be returned to storage and subsequently disposed of when authorised by the study director or management. Any changes of storage location must be recorded.

During sample processing and analysis, containers of dilutions, extracts, *etc.* must be unambiguously identified. If, due to practical problems, *e.g.* small container size it is only possible to label the container using a short-code format there must be a mechanism to ensure that traceability to the parent sample is maintained.

Special attention should be given to samples placed in small vials, *e.g.* for HPLC/GLC/NMR analysis. These vials should be identified by a label or by other appropriate means, *e.g.* indelible pen. Where autosamplers containing many samples are in use, it may be advisable to record the position of the vials on a sample analysis record and to consider uniquely identify the carousel (*e.g.* with study number).

Bar-code systems can be used to assist sample identification or traceability; however, use of these systems should be fully validated and documented.

**21.2.7.4 Preparation.** In some situations, it is necessary to process an initial bulk sample to produce a homogeneous laboratory sample of reduced size, which is convenient for further storage and analysis. Sampling procedures must preserve sample integrity, such that it remains representative of the original bulk sample.

Provision should be made to ensure that sample mix-ups or cross contamination cannot occur. This is likely to be achieved by the provision of adequate space, careful planning of the utilisation of space and good laboratory-management processes. To avoid confusion, separation of similar laboratory operations from different studies in space or time is recommended.

The stability of samples during the period of storage and subsequent analysis should be considered.

Sampling procedures whether routine or specialised should be documented in the study plan or standard operating procedures.

**21.2.7.5 Analytical Methodology.** Analytical methods may be study-specific and detailed in the study plan or can be general procedures described in standard operating procedures or other documents such as published references.

The analytical methods should be described in sufficient detail such that an appropriately qualified or experienced scientist or technician can undertake the work.

Each analytical method should be appropriately validated for its intended purpose. Guidelines exist which describe the requirements for the validation of analytical methods to be used in the generation of data for specific regulatory purposes. Where specific guidelines are not available, validation data/records should include but not necessarily be limited to precision and accuracy, specificity, range, linearity, limits of quantification (detection).

**21.2.7.6 Data Recording.** Data generated in an analytical laboratory might be in the form of hand-written entries into a laboratory notebook, a loose leaf system or a computer-generated format. To ensure that an audit trail exists there should be an appropriate system of cross-referencing so that all data relating to a study can be formally identified.

Where a hard-backed notebook is dedicated to one study the book should be uniquely identified with the study number and page numbering is recommended.

If a notebook is used for a number of different studies, there must be unambiguous identification of the study or studies to which all entries relate.

If a notebook is in loose-leaf format the individual pages must be uniquely identified with the study number and page numbering is recommended.

Printouts from analytical instruments must reference the study and samples to which they relate and be dated and signed. Where possible, printouts should be identified prior to generation of the data and should be removed promptly on completion of analysis.

Note that for frequently carried out activities the use of proformae is recommended.

Special criteria apply to data that is generated/stored as electronic records/signatures by a computerised system. In these situations, laboratories must have policies and procedures in place to ensure that the prevailing criteria, for the acceptance of the electronic records/signatures as the equivalent of paper records/signatures by the regulatory authorities, are met.

### 21.3 REPORTING OF RESULTS

The reporting arrangements will depend on whether the analytical work undertaken formed part of a study, or whether it was a separate study (Chapter 18).

If the analytical work constitutes a complete study there should be a final report containing the essential information required by the principles of GLP. Where a particular type of study or a series of studies is performed frequently in the laboratory, it may be appropriate to prepare a standardised final report containing the majority of general information required and authorised in advance by the testing facility management. Study-specific extensions to such reports (*e.g.* with details of the test material and the numeric results obtained) may then be issued as a supplementary document requiring only the dated signature of the study director.

Any data generated by a facility not included in a national GLP compliance monitoring programme must be fully identified (on the GLP compliance statement) by the study director.

If the analytical work was the responsibility of a principal investigator, that person is responsible for the production of a report detailing the work carried out under his/her supervision and for sending the report to the study director. There should be a statement signed by the principal investigator certifying that the report accurately reflects all of the work performed and results obtained, and that the work was conducted in compliance with the principles of GLP. The principal investigator may present the original raw data as his/her report, accompanied by a statement of GLP compliance.

If the work was conducted by a subcontractor laboratory, there should also be a QA statement signed by that laboratory's QA unit.

The report(s) of the principal investigator(s) can be attached to the overall study report by the study director as appendices.

#### 21.3.1 Archives

After completion of the laboratory activities or on completion of the study, all raw data, specimens, the study plan, the final report and other relevant documentation, *e.g.* maintenance records should be retained in the archives (Chapter 36). Where analytical methods have followed published references or test guidelines, copies of these references or guidelines must also be retained.

Where laboratory notebooks or other records contain data relating to a number of different studies it may be necessary to produce authenticated copies for inclusion in individual study files. The original notebooks/records should be transferred to the archives within a specified period.

*Note:* The printouts from some analytical instruments are produced on heat-sensitive paper, in which print is known to fade and become illegible with time. In these situations authenticated copies should be taken to ensure long-term storage of the data.

### 21.4 REGULATORY ISSUES

The application of regulatory guidances/guidelines, which detail specific requirements as to study conduct and documentation for the submission of bioanalytical data should be differentiated from the 'compliance' requirements of GxPs, *i.e.* GCP, GLP and GMP. In addition any study submitted to the FDA should comply with 21 CFR Part 11(REF), the intricacies as to how these requirements can be met have been the subject of many meetings/presentations and publications although not all



have been directly relevant to bioanalytical studies. Thus 21 CFR 11, which pertains to electronic records and electronic signatures should be applied to any system regardless of the implementation of GXP.

In February 2002, the FDA withdrew the Draft Guidance while it re-examined 21CFR11 as it applies to all FDA programme areas. This re-examination may result in revisions to Part II but in the meantime the FDA provided some broad guidances as to how the requirements of 21CFR11 should be interpreted contingent upon the FDA reissuing guidance documents; as such the reader should make themselves fully aware of the FDA **current** requirements.

The withdrawal of the Guidance reflects industry concerns about its ability to meet the requirements – especially with respect to interpreting the requirements for validation, audit trails, record retention, record copying and legacy systems. This has been further complicated by statements made by agency staff being interpreted as statements of agency policy.

For example the use of an audit trail in chromatographic systems which monitor each and every change in interpretation of the baseline, requiring full “electronic” signature is not user friendly and may add little to the overall integrity of study. That some form of audit trail needs to be defined is a basic requirement of GXP, *e.g.* the first baseline interpretation by the computer and the final baseline used to generate data which is reported/documented may be a good starting point. Indeed, the extent and nature of documentation should largely be based on risk assessment, a concept currently embraced by the FDA not only for c-GMPs but also used to evaluate submissions. Until recently the FDA set specifications and standards and reviewed documentation and inspected against these standards, whereas the current approach is to evaluate the value of the data in the context of the study design with respect to its impact on the safety of the final product.

#### 21.4.1 Instrument Qualification and Validation

The instrumentation used for both GMP and GLP studies must be fit for purpose. Although there are differences in the wording of GLP and GMP requirements as to what is expected, *e.g.* The UK's MCA Orange Book incorporating the EU GMP Registration Annex 15 page 182 requires equipment, which is critical for the quality of the products, to be subjected to appropriate qualification. While the FDA GLP regulations require that equipment, which is used for generation, measurement or assessment of data, is adequately tested, calibrated and/or standardised.

There is however, a developing trend to apply the GMP requirement to qualify equipment more rigorously to GLP studies, although, as detailed above the GLP guidelines are not rigorously defined. The qualification process is generally divided into a number of stages, *i.e.* Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ). A pragmatic approach to instrument Qualification has been discussed by Freeman *et al.* in their position paper on the Qualification of Analytical Equipment. Qualification is the responsibility of the end user and is designed to ensure that the equipment is both fit for the purpose and continues to function so, over the ‘lifetime’ of the equipment. Responsibility cannot be abrogated to the supplier. This does not however, prevent suppliers providing help in the form of protocols and targeted servicing.

It has been suggested that standard terminologies and approaches for the GLP GMP and GCP laboratories should be developed and published. One concern widely expressed was that terminologies used for instrument qualification and software validation had become interchangeable. This has been further complicated by the fact that much (most) current analytical equipment is driven by software either as firmware or by interfacing with computer systems using integral software either as part of the instrumentation or produced by a third party. In such cases it was felt that equipment should be qualified and the term validation be restricted for processes, *e.g.* methods are validated.



In general IQ and OQ are User/Vendor driven while PQ is the responsibility of the user. One approach is:

- Do your homework prior to instrument purchase. Instrument purchase should focus on suitability for intended use – emphasizing the need not to rely on FDA or Consultants for the science – *i.e.* User Requirement Specification (URS).
- IQs should clearly identify calibration, maintenance, SOP (how to use it) and training needs.
- OQ should ensure proper function of all system components.
- PQ should ensure suitability of the “entire” HPLC system.
- Methods should be developed and validated using appropriate (relevant) system suitability tests (SSTs).

SST failures would suggest a troubleshooting process involving PQ (holistic) approach and if necessary OQ (modular) approach to identify problems and initiate resolution, *e.g.* repairs or change of pump injector, plumbing, *etc.*

Application to other study types, particularly bioanalytical studies, is at the bench level similar in many respects to the process already described. However, specific guidance for Industry has been published by the FDA in their Bioanalytical Methods Validation for small molecules but similar guidance for macromolecules has yet to appear.

## 21.5 BIOANALYTICAL METHODS VALIDATION

This is perhaps the most complex area in terms of applicability of GLP, GMP or GCP. Similarly the “FDA Guidance for Industry, Bioanalytical Methods Validation BMV”, can be implemented in a GLP or non-GLP environment; implementation of this Guidance is *not* synonymous with GLP. Indeed, in the context of the FDA, bioanalysis is an integral part of non-GLP based guidances, *e.g.* 21CFR320 – Bioavailability and Bioequivalence Requirements (Drugs for Human Use). A similar EU document, CPMP Note for Guidance – has recently been published and has a requirement for bioanalysis to be carried out according to the *principles* of GLP. It should be noted that this is NOT the same as requiring such studies to be done to GLP. It is however expected that study plans/protocols be prepared, audit trails for all processes and data generation should exist.

### 21.5.1 Compliance with GLP?

ICH-S3A; Toxicokinetics: Guidance on the assessment of systemic exposure in Toxicity Studies requires the application of GLP to both the toxicological aspects of the study and related bioanalysis and the reader is referred to Chapter 12.

GLP was developed as a consequence of inadequacies in *preclinical* studies, although as it is now defined, it applies to non-clinical studies. As a consequence the application of a bioanalytical method to a toxicokinetic study should be carried out in compliance with GLP. However, when it comes to the validation of a bioanalytical method the requirement to carry out these aspects in compliance with GLP is debatable. Indeed in both the UK and Japanese regulations validation is considered a non-GLP activity, although a preference that it should be carried out in a GLP environment is self evident throughout the industry. Furthermore, bioanalytical methods for human bioavailability (BA), bioequivalence (BE), pharmacokinetic studies (PK) and drug-interaction studies must meet the criteria of 21 CFR 320.29 and are essentially not covered by GLP; on the other hand the FDA Bioanalytical Methods Validation Guidance states “The analytical laboratory conducting BA and BE studies should “closely adhere” to FDA’s GLPs and to sound principles of QA throughout the testing process”. The legal claim ‘compliance with GLP’ is replaced with the term should ‘closely adhere to FDA’s GLPs’. Many laboratories have developed similar ‘statements’ which while not claiming compliance with GLP – claim processes are in

operation that are closely related to it, *i.e.* “This study was carried out in laboratories which are GLP certified” or “This study was carried out in accordance with the principles of GLP”. These terminologies are reflected in the CPMP note of Guidance on the Investigation of Bioavailability and Bioequivalence (REF), where it states that the bioanalytical part of BE trials should be conducted according to the applicable principles of GLP but note, NOT compliant with GLP.

The FDA 21 CFR Part 320 Bioavailability and Bioequivalent Requirements (Drugs for Human Use) [36] are somewhat less definitive about the bioanalytical requirements, *i.e.* 21 CFR 320.29, states “The analytical method used in an *in vivo* bioavailability study to measure the concentration of the active drug ingredient or therapeutic moiety, or its metabolites in body fluids or excretory products or the method used to ensure an acute pharmacological effect shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision the actual concentration (accuracy?) of the active drug ingredient or therapeutic moiety or its metabolites achieved in the body.”

However, this predates the BMV Guidance (REF), as such the latter document amplifies these requirements, which are reiterated in the FDA’s compliance manual (REF) for inspecting BA and BE studies, *i.e.* “The analytical laboratory should have a written set of standard operating procedures (SOPs) to ensure a complete system of quality control and assurance”. The SOPs should cover all aspect of analysis from the time the sample is collected and reaches the laboratory until the results of the analysis are reported. The SOPs should include record keeping, security and chain of sample custody (and integrity).

Pragmatically the application of GLP in the context of the bioanalytical laboratory at the operational level should satisfy the requirements of studies from all areas of the drug development process, although compliance is only required and possible for preclinical studies. While it is inappropriate to claim compliance with GLP for clinical studies it would appear difficult for laboratory procedures to be carried out under different codes. As such attempts to harmonise the GXP’s, at the laboratory level, would appear to be the rational way forward. A major driver in this respect is the implementation of the FDA’s electronic records and signatures requirement under 21CFR 11, which applies equally to GLP, GMP and GCP. Similarly, a standardised approach to instrument qualification would seem to make practical sense as discussed earlier.

The FDA’s Reviewers Guidance in 1994 for evaluating/reviewing analytical methods applies to both bioanalytical and pharmaceutical analytical studies. Recently The British Association for Quality Assurance (BARQA) developed some tentative Good Clinical Laboratory Practice (GCLP) Guidelines, to encompass all laboratory- based activities that support clinical studies in safety clinical chemistries and for the bioanalytical support of pharmacokinetic and pharmacodynamic studies. It would seem appropriate therefore to embrace this trend and to develop requirements for analytical laboratories which cross the GXP’s.

Guidance represents the best Scientific judgement and current thinking, it is informal and nonbinding. It does not create or confer any rights for or on any person and does not operate to bind FDA or public. An alternative approach may be used if such an approach satisfies the requirement of the applicable statute, regulation or both.

## 21.6 BIOANALYTICAL VALIDATION PROCESS

Full method validation is required for a new drug entity and when implementing a developed method for the first time. Importantly the guidance stresses the need to fully validate a method when a “new” metabolite is identified and needs to be quantified to determine its kinetics. Validation of a bioanalytical method comprises two distinct phases:

- (i) The pre-study phase in which the characteristics of the assay with respect to stability, specificity (selectivity), accuracy, precision, limits of quantification (sensitivity) and response function are determined.

- (ii) The study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the bio-study mainly in order to confirm the stability, accuracy and precision, *i.e.* the method performs to the same characteristics as the validated method.

The Guidance defines two additional types of validation:

- (i) Partial validation recognises that when modifications are made to a fully validated method, the impact of these changes on the integrity of the methodology should be fully addressed. The practical implication of changing methodology and circumstances necessitating such changes are discussed.
- (ii) Cross validation is defined as the comparison between two or more different bioanalytical methods or perhaps more importantly a comparison between different sites or laboratories. This is essential when data from different sites are generated for the same study.

### 21.6.1 Full Validation

**21.6.1.1 Prestudy Phase.** Bioanalytical method validation includes all the experimental procedures and documentation of such that demonstrate that a particular method used for quantitative measurement of analytes is reliable and suitable for the intended analytical applications. Fundamental parameters that require determination are accuracy, precision, selectivity, sensitivity, reproducibility and stability. When considering the requirements for validation, in terms of suitability for use, it is important to understand the significance of the how analytical data impacts on the overall interpretation and objectives of the study. For example, validation requirements, in terms of precision, accuracy, specificity, *etc.* validation may be significantly different for methods required to analyse samples from human BE studies, where biological variability is less (serial sampling for the same subject, cross-over designs) compared to that of animal toxicokinetic studies, or analysis of tissue samples, where biological variation will be much greater (single sampling from individual animals).

The specific recommendations for method validation for chemical assays are given in the Guidance.

Thus, matrix-based calibration/standard curves for each analyte should consist of a blank sample (matrix sample without internal standard), a zero sample (matrix sample spiked with internal standard) and 6–8 non-zero standard points (concentrations), covering the entire concentration range and including the lower limit of quantitation (LLOQ). Throughout the guidance various numbers of standard points required to define a standard curve are quoted. In principle, additional points, ( $n > 6$ ) should be included, particularly for non-linear relationships. The simplest model that adequately defines the concentration–response relationship should be used and the *goodness of fit* in terms of back-calculated responses of the individual concentrations should not deviate by more than 15% from the nominal concentration (20% at the LLOQ). The selection of weighting and the use of a more complex regression model should be justified. At least four out of six non-zero standards should meet the acceptance criteria, including the LLOQ and the highest calibration standard. Excluding standards should not change the model used. If the number of standard concentrations is greater than six, 75% or a minimum of six non-zero standards should be acceptable.

Accuracy as determined by replicate analysis of spiked samples containing known amounts of analyte should be measured at minimally four concentrations over the entire calibration range (low (up to  $3 \times \text{LLOQ}$ ), middle and high concentrations), as well as at the LLOQ of the method. A minimum of five determinations per concentration is required during a single analytical batch to

establish within-batch accuracy. Inter-batch measurements should be determined by analysis of quality control (QC) samples at the same concentrations on separate occasions (minimally three). The mean measured concentration should be within 15% of the actual concentration except at the LLOQ, where it should not deviate by more than 20%. The deviation of the mean from the true value being a measure of accuracy.

Precision, in terms of the closeness of agreement between measurements from multiple sampling of the same homogeneous sample, should be determined at a minimum of three concentrations and at the LLOQ of the method, at the concentrations defined for accuracy determination. A minimum of five determinations at each concentration within a single batch should be undertaken to establish within-batch precision. Inter-batch precision or repeatability, measuring precision over time (minimally three occasions), which may involve different analysts, equipment, reagents and laboratories, if appropriate, should be determined. The precision determined at each concentration should not exceed 15% coefficient of variation (CV), except at the LLOQ, where it should not exceed 20%.

Selectivity from potentially interfering substances (endogenous compounds, metabolites, decomposition products, and concomitant medication) should be established by the analysis of blank samples of the appropriate biological matrix obtained from at least six different sources. Each sample should be checked for interference to ensure selectivity at the LLOQ of the method for each analyte. No absolute criteria are set, except that the analyte response at the LLOQ should ideally be at least five times the response compared to the blank response. In the case of hyphenated mass spectrometry-based methods, test for interference may be less important, however matrix effects which may compromise the ionisation of the analyte should be investigated to ensure that precision, selectivity and sensitivity is not compromised.

Stability of each analyte in biological matrix should be confirmed, minimally at low and high concentrations (at least three replicates at each concentration) over the calibration range, during short-term storage at room temperature. The storage time should be based on the expected duration that test samples are maintained at this temperature during the intended study (4–24 hr). Stability should also be determined after three freeze and thaw cycles and after longer-term storage in the freezer, on three separate occasions, using identical storage conditions to those of the test samples (*i.e.*  $-20$  or  $-70^{\circ}\text{C}$ ). Long-term storage should confirm stability over the longest period which test samples are stored, ideally prior to analysis.

Stability of each analyte and internal standard stock solution, if appropriate, should be evaluated at room temperature for at least 6 hr, and if refrigerated or frozen, during a relevant storage period. Stability should be tested by comparing the instrument response of the old solution with that of a freshly prepared solution. Once stability has been confirmed and accuracy of preparation verified, standards and QCs can be prepared from the same spiking stock solution.

The stability of processed samples, including residence time in the autosampler should be determined for the length of the anticipated batch size and to cover re-injection of samples, if appropriate. For labile analytes, investigations may include analysis of samples from dosed subjects.

The guidance states that concentrations of all stability samples should be compared to the mean of the back-calculated values for the samples, at the appropriate concentrations, measured on the first day of testing. The disadvantage of using this approach, instead of comparing measured values with the theoretical (nominal) spiked concentration, is that error measurements (which can be as much as  $\pm 15\%$  for each measurement) may make interpretation difficult. Generally speaking, if stability is a problem then a loss of compound with time should be evident (*i.e.* trend in gradually decreasing concentration). When using a comparison with theoretical concentrations, stability will only become evident when accuracy measurements exceed the 15% error criteria.

The ability to dilute samples whose concentrations are above the upper limit of quantification (ULOQ) of the method both accurately and precisely should be demonstrated. This can be achieved

by preparing a QC sample at a concentration higher than the anticipated maximum concentration expected in test samples (*i.e.*  $10 \times$  mid-point of calibration line) and diluting this sample 10-fold with the same biological matrix prior to analysis. The precision and accuracy of the measurement of this sample should meet the criteria previously discussed. Once the dilution has been validated the need to incorporate actual within-study over-range QC samples is obviated.

**21.6.1.1.1 Application of the Validated Method.** Once the method has been validated for routine use, its precision and accuracy should be monitored regularly to ensure continued performance. Matrix-based calibration curves, consisting of a minimum of six non-zero standard points (either single or replicate) and QC samples at a minimum of three concentrations (low, middle and high), at least in duplicate, over the calibration range should be analysed with each batch of test samples.

The response function of the calibration curve, in terms of curve fitting, weighting and goodness of fit, should be the same as used during the validation phase. System suitability is used to ensure optimum operation of the analytical system.

Results of the matrix-based QC samples are the basis of accepting or rejecting batches. For a batch to be accepted, at least 67% (four out of six) of the QC samples should be within 15% of their respective theoretical values. This means that 33% of the QC samples may be outside the  $\pm 15\%$  criteria, but there must be at least one QC at each concentration level within 15% of its theoretical value. The minimum number of QC samples (in multiples of three) analysed in a batch should represent 5% of the total number of unknown samples or a minimum of six, whichever is the greater.

Estimations above the upper level of quantitation (ULOQ) or below the LLOQ are not recommended, high-level samples should be diluted with matrix on to the validated calibration range.

In the case of multiple analytes, data from only one analyte failing the acceptance criteria should not preclude acceptance of data for the other analytes, which are acceptable.

Where samples need to be reanalysed or reintegrated a guideline or SOP should be in place to explain the rationale for these procedures.

**21.6.1.1.2 Study Documentation.** All validations and sample analyses should adhere to FDA GLPs. General and specific SOPs and good record keeping are essential to support regulatory submissions.

Documentation requirements for method establishment and validation should provide a detailed operational description of the analytical method, including the purity and identity of the reference standards (compound, metabolites, internal standard, if appropriate) used. In addition, a description of all validation experiments and the relevant data obtained in these studies are required and this also includes stability studies.

Documentation should include legible examples of annotated chromatograms or mass spectrograms, if appropriate. It should also include any deviations from SOPs, protocols and GLPs, if applicable and justifications for deviations.

Documentation to support the application of the validated methods should again include the purity and identity of the reference standards (compound, metabolites, internal standard, if appropriate) used. Chain of custody of the samples, in terms of sample identification, collection dates and times, storage conditions prior to and after shipment and their condition and storage prior to analysis should be documented and tabulated.

Summary tables of analytical batches should include, batch (run) identification, date and time of analysis, method, analyst, start and stop times, duration, significant equipment and material changes, issues or deviations from the established method.



All calibration curve data, including equations used for back-calculation of results, QC sample summary and data on inter-assay accuracy and precision from calibration curves and QC samples used for accepting analytical batches should be available.

Representative complete serial chromatograms of test samples including standards and QC samples, representing 20% of subjects for pivotal BE studies are required. In other studies, 5% of randomly selected subjects in each study should be included. The selected chromatograms should be defined prior to sample analysis.

Reasons for missing samples, repeat analysis of samples and reintegration of data should be documented. Information should include the initial and repeated result, reason for the repeat, requestor and authoriser for the reanalysis. Repeat analysis and reintegration should be undertaken using predefined SOPs.

All deviations from the analysis protocol or SOPs, with reasons and justification should be documented.

## 21.7 GMP IN THE ANALYTICAL LABORATORY

Regulations governing the manufacture and distribution of medicinal products require that the holder of a manufacturing authorisation establishes a system of QA. The objective is to ensure that the medicinal products are fit for their intended use, comply with the requirements of the marketing authorisation and do not present risks to the patient and public in terms of safety, quality and efficacy. The system of QA must incorporate GMP; a set of principles and guidelines designed to ensure that medicinal products are manufactured and controlled to appropriate quality standards. Inherent in GMP is the process of QC, which includes the sampling, testing, specification, organisation, documentation and release procedures associated with the development and manufacture of medicinal products. These are discussed further in Part 3 of this book.

The functions associated with QC, including release of batches and stability testing, are carried out in the analytical laboratory and, as such, GMP must be applied in these laboratories. In this context, QC should be seen as a term covering not only laboratories involved in batch release testing, but also development laboratories involved in functions such as methods validation and stability testing.

While the focus of GMP regulations is the manufacture and control of medicinal products, achieving the quality objective requires the application of GMP not only to testing of the final product but also to other aspects which can affect quality. The objective is to ensure that quality is built in throughout the process of developing, producing and distributing a medicinal product, *i.e.* it is not something that can be added at the end of the process by QC testing alone. As a result, GMP makes specific demands in terms of the people, facilities, equipment, materials, processes and methods involved in the manufacture and control of medicinal products. These demands must also be satisfied in the conduct of certain aspects of a product's development, such as stability testing and methods validation.

In contrast to GLP guidelines, GMP regulations and guidances provide substantial advice on the application of GMP in analytical laboratories, referred to as Good Quality Control Laboratory Practice. However, there remains a need for expansion and elucidation of the requirements in order to provide the detailed instructions for achieving compliance in the laboratory. Furthermore, in recent times, the application of GMP regulations has been extended and is no longer confined to licensed products. Recent developments have seen GMP applied to the manufacture and release of materials for clinical trials (investigational medicinal products, IMPs) and to active pharmaceutical ingredients (APIs). This brings many more analytical laboratories into the GMP environment and provides further impetus for the provision of practical guidance in applying GMP principles in the laboratory.

### 21.7.1 When to Apply GMP

The work of the analytical laboratory covers many aspects of the development, manufacture, control and release of medicinal products. Many of the functions of the analytical laboratory result from or are covered directly by GMP regulations. Other functions are not specifically identified in GMP regulations, but must by implication be undertaken in compliance with GMP. It is important to understand and identify which types of testing should be performed to GMP.

The types of testing undertaken in an analytical laboratory can be categorised generally as follows:

- Batch release testing (testing products to ensure compliance with specification), which includes in-process testing and applies to products for market and those for clinical trials.
- Stability testing, in support of licence applications for both final products and clinical trials materials.
- Validation support activities, such as methods validation, process validation, cleaning validation and establishment of reference materials.
- Development activities, such as compound characterisation, excipients compatibility trials, formulation development support and other discovery and early development phase investigations.

Figure 1 provides a general indication of where various analytical activities occur in the development life cycle of a medicinal product.

It is clear that testing such as batch release and stability trials in support of product-licence applications should be conducted in compliance with GMP, as these are specifically cited in GMP regulations and guidance. In addition, GMP requires that release of batches is supported by validated processes, methods, specifications and sampling procedures and therefore by inference, validation activities applied to, for example, methods, manufacturing processes and cleaning processes, should also be carried out in compliance with GMP.

However, the decision as to when to apply GMP to development activities is less clear-cut. Ideally, the discipline of GMP could be applied to all analytical operations, thereby providing a high level of assurance as to the value and quality of the data produced and avoiding some repetition of testing in later development phases under GMP conditions. However, it is recognised that this could create unnecessary cost and delay and could stifle innovation, especially in the discovery and early development phases of a product's life cycle. Consequently, it is acceptable and inevitable that some supporting data provided in licence applications will have been generated in non-GMP compliant environments. In general, GMP is applied to most types of analytical work undertaken from the point at which data supporting the stability and specifications of Phase I clinical trials materials are generated.

In identifying when and where to apply GMP, consideration should be given to the potential deleterious effects of operating different standards within a single laboratory or analytical team. This could occur where, for example, stability studies and early compound or product-development support are being conducted in the same laboratory. Operating to different standards by applying GMP principles to the stability studies and not to the development support could cause confusion in the minds of the analysts. This might lead to error and a reduction in quality, which could be critical for the GMP work. In cases such as this, it is usually beneficial to apply the same standards, *i.e.* GMP standards, to all of the work being performed (although claims of compliance with GMP would only be made for the work which officially requires such a claim).

### 21.7.2 GMP on the Laboratory Bench

In many instances, general guidance available amounts to broad directives rather than the specific practical measures which this chapter aims to provide. At the laboratory bench, in the course of



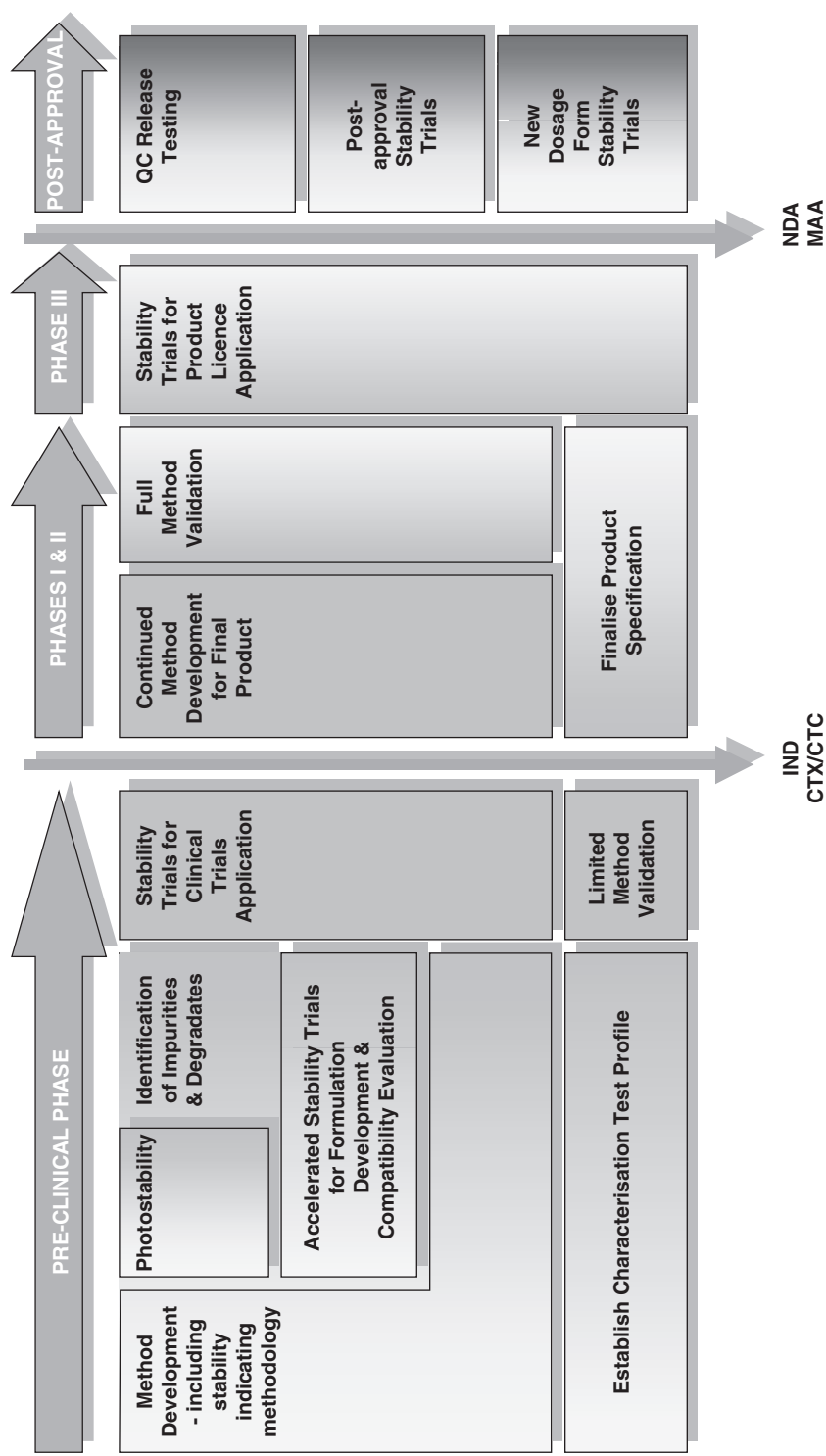


Figure 1 Typical analytical development programme

day-to-day testing, the application of GMP results in procedures which are very similar or, indeed, identical to those described above under GLP. Indeed, it should be expected that the outcome of regulations, principles and guidelines, designed to achieve quality in laboratory operations, is a very similar set of procedures. There are however, some areas in which GMP requirements differ from those of GLP and some requirements of GMP which are not reflected or appropriate in the GLP environment as discussed below.

### 21.7.3 Differences Between GMP and GLP

In comparing and contrasting GMP and GLP, it is apparent that the major difference lies in the manner in which the work under each practice is organised and managed. GLP is focused on the concept of a study, which is a self-contained investigation with specific documented objectives, procedures and reporting requirements, described in a study plan. The GLP study has one study director (with responsibilities laid down in GLP regulations), one study plan and one final report. However, GMP is focused on and driven by the eventual release for market or clinical trial of a drug product or the certification of a drug substance. Therefore, GMP documentation is generally batch related, resulting in the issue of Certificates of Analysis, although some development work, such as methods validation, may be documented in discrete reports. Importantly, GMP does not have the concept of a study director, but it does contain very explicit requirements on quality management and, in the case of European regulations, requires certification of each batch of a drug product by a Qualified Person (with responsibilities and duties laid down in European GMP regulations). While Management has the same quality objective in both GMP and GLP environments, its specific responsibilities and organisation differ between them.

In addition, QA is manifested somewhat differently in each environment. In GLP, QA is described as a functional unit which must be discrete from and independent of the operational unit(s), including the analytical laboratories. However, in GMP regulations, QA is described as the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the required quality. QA includes GMP and QC. Effectively, the GMP analytical (QC) laboratory is an executive component of the QA function. In other words, it is the analytical laboratory, as a component of the QC function, which must be independent (of the production function).

The responsibilities of GMP QC also extend beyond the analytical laboratory to include, for example, reviewing production records, verifying labelling of containers, obtaining representative samples for analysis and participating in the investigation of product complaints. These duties require the staff of a GMP analytical laboratory to leave the laboratory to undertake duties in other functional areas.

There are also differences in the manner in which testing is organised and carried out at the laboratory bench. For example, with GLP formulation analysis or bioanalysis, it is generally possible to obtain unmedicated samples to test as controls and fortified (spiked) samples with each set of samples, thereby performing what amounts to a mini validation on each analytical occasion. This is rarely possible when testing drug substances and products routinely in the GMP environment. Consequently, much greater emphasis must be placed on ensuring that the component parts of testing (*e.g.* equipment and test methods) are operating according to specifications.

These differences have a number of practical consequences for those working in an analytical laboratory which is operating in compliance with GMP. The following sections detail the measures which should be implemented in addition to or instead of those detailed in the GLP section. The items covered are:

- Management and organisational arrangements
- Sampling and retention of reserve (reference) samples
- Test Records
- Training programme

- Qualification, validation and change control
- Qualification of equipment
- Methods validation
- Out of Specification (OOS)/Out of Trend (OOT) procedures
- Self inspection
- Archiving periods

*21.7.3.1 Management and Organisational Arrangements.* A cornerstone and key requirement of GMP is that the Head of Production and the Head of QC must be independent from each other. The Head of QC will normally have direct control of the analytical laboratories performing batch-release testing.

In some cases development laboratories, in which operations such as stability testing and methods validation may be undertaken, will be within an organisational area which is separate to the production and control areas of a company. These laboratories may not be under the control of the Head of QC, but it is advisable that the manager of analytical-development laboratories is also independent from Production, as these laboratories may be involved in obtaining representative samples for stability tests and other investigations.

In general, the Head of QC has responsibility for; approving or rejecting starting materials, packaging materials and intermediate, bulk and final products; evaluating batch records; ensuring that all necessary testing is carried out; approving specifications, sampling instructions, test methods and other QC procedures; approving and monitoring contract analysts; checking the maintenance of QC facilities and equipment; ensuring that appropriate validations are done and ensuring that the required initial and continuing training of QC personnel is carried out and adapted to need. The Head of QC may, and generally will, delegate some of the functions associated with these responsibilities (though not the responsibilities themselves) to the staff of the analytical laboratory.

It should be noted that in European regulations, a Qualified Person (QP) must certify each batch of medicinal product prior to its release. The QP function may be fulfilled by the Head of QC or by the Head of Production or, indeed, by a third person, provided that that person has the necessary qualification requirements as laid down in the legislation.

*21.7.3.2 Sampling and Retention of Reserve (Reference) Samples.* Usually, sampling will be conducted or supervised by appropriately trained personnel from the analytical laboratory, who will enter production areas for this purpose. Documentation should include a Standard Operating Procedure (SOP) for obtaining representative samples from bulk or finished pharmaceutical materials and products and this SOP should be approved by QC. This procedure should document the method and equipment to be used, the amount of sample and any sub-samples (including the method of any sub-division), the type of containers, identification and storage conditions to be used for the (sub-)samples and the method of cleaning and storing the sampling equipment.

As well as the samples removed for batch release testing, it is necessary to obtain reserve (or reference) samples. Reserve samples of APIs and other starting materials should also be retained. The relevant national regulations and guidances should be consulted to ascertain the required periods of retention of reserve samples and the required amounts to be retained.

*21.7.3.3 Test Records.* Analytical records in the GMP environment are generally related to a particular batch of a medicinal product or drug substance. The records should include the name of the material or product and, where applicable, the dosage form; the batch number, site of manufacture and the unique product code, where applicable; references to the relevant specifications and test methods; test results, including observations and calculations, and reference to any

Certificates of Analysis; dates of testing; identity of persons performing the testing; identity of persons verifying the testing and calculations and, finally, a clear statement of release or rejection (or other outcome) attested by the responsible person.

**21.7.3.4 Training Programme.** The personnel involved in GMP operations must have the appropriate qualifications, training and experience for the duties that they are expected to perform. For each individual, records should be maintained to demonstrate these attributes. Details of relevant qualifications, courses attended and experience (perhaps in the form of a *Curriculum Vitae*, CV) should be held, together with current and superseded job descriptions. A training record should be maintained, recording details of training given and the outcome of evaluation of competency with respect to each duty or task. It may also be appropriate to record an individual's capability to train and evaluate the competency of others.

GMP regulations specifically require that training programmes should be established, in addition to the maintenance of training records. Training programmes for personnel in the analytical laboratory should be approved by the Head of QC (or equivalent in a development laboratory). The purpose of training programmes is to ensure that training is directed to the needs of both the organisation and its staff. It may be appropriate to establish a generic training programme, corresponding to the career-development path. Based upon the generic programme and individual performance, personal training programmes may then be developed to ensure that each individual receives training that is appropriate to needs.

An essential part of the training required is instruction on the theory and practice of GMP. As well as basic training in this respect, continued training should be provided throughout each individual's employment. Training should also be provided in respect of the processes, procedures, tasks and analytic techniques that will be utilised by the individual.

Taken together, the above measures should ensure that personnel are qualified for the duties which they are to perform and that there is proof of this qualification.

**21.7.3.5 Qualification, Validation and Change Control.** Qualification and validation are critical functions within the GMP environment. Qualification may be seen as ensuring that the items that will be used in a process, such as equipment and materials, are suitable for their intended purpose. Validation may be viewed as ensuring that a process itself produces the intended outcome in an accurate and precise manner. Both qualification and validation procedures should be described in a Validation Master Plan (VMP). A VMP may be specific or it may be generic. It should include; reference to validation policy; organisational structure of qualification/validation activities; summary of facilities, systems, equipment and processes to which it is to be applied; documentation format for protocols and reports; planning and scheduling; change control and reference to any other existing relevant documents. In approaching qualification and validation, it is prudent to address the question of what should be qualified and validated, with what frequency and what re-qualification or re-validation may be required following change.

The decision of when to apply qualification and validation or re-qualification and validation and the extent of the procedures applied should be based upon assessment of the risk to quality posed by the equipment or process or any changes to these.

Qualification is relevant for equipment which is critical for the quality of the products. In the analytical laboratory, this would apply in general to any measuring, weighing, recording, storage and controlling equipment, for example, balances, thermometers, HPLCs, dissolution equipment, image-capture systems and freezers. Generically, this equipment may be referred to as "instruments". Non-critical equipment may include items such as magnetic stirrers and water baths. Generically, this equipment may be referred to as apparatus and qualification need not be applied.

Validation is relevant for processes which are critical for the quality of the products. In the analytical laboratory, this would apply primarily to test methods. However, the analytical

laboratory will provide a key contribution to the validation of manufacturing processes and cleaning procedures.

Once all of the equipment and processes in a system have been qualified or validated, it is necessary to ensure that they remain so. As a result, it is appropriate to maintain a system for identifying and controlling changes or modifications and to re-qualify or re-validate following critical changes. It may also be appropriate to re-qualify equipment at regular defined intervals, in order to detect any age related deterioration which could occur. With both equipment and processes, it is usual to put in place checks of performance to ensure that they continue to operate within acceptable limits following qualification or validation. Examples of such checks in the analytical environment are system suitability tests (SSTs) for test methods.

*21.7.3.6 Qualification of Equipment.* Equipment used in the GMP analytical laboratory should be designed, located, qualified, calibrated and maintained to suit its intended purpose. Equipment qualification is comprised of four components. The first of these components, Design Qualification (DQ) is not usually applied in the analytical laboratory as equipment is usually purchased “as designed”, without modification. However, as the end user, the responsibility to ensure that the manufacturer has demonstrated compliance of the design with GMP or similar quality standards, such as ISO 9000 series, rests with the laboratory management. Usually, DQ may be replaced by a user requirement specification (URS), which defines the required functional and operational specifications of the equipment and, where appropriate, any training and maintenance requirements.

Once received, equipment should be subjected to the remaining components of qualification, as follows:

IQ – establishes that the equipment is received as designed and specified, that it is properly installed in the selected environment and that this environment is suitable for the operation and use of the equipment. Appropriate actions may include:

- Ensuring that equipment (including software and firmware) matches the purchase order and delivery note and that any pre-delivery checks have been done.
- Recording serial numbers, firmware/software versions,
- Ensuring that environment, location and facilities are appropriate.
- Assembling and ensuring that equipment powers up and passes any self-checks.
- Ensure that relevant operating manuals and SOPs are in place.

Operational Qualification (OQ) – demonstrates that equipment will function correctly according to its operational specification in the selected environment. The equipment should be tested against critical performance specifications as specified in the URS. Equipment should always be calibrated prior to performing OQ tests and, where possible, traceable calibration and verification tools should be used. Appropriate actions may include:

- Validation of any software applications.
- Evaluating key functions of the equipment.
- Use of non-method-specific calibration and verification checks.

Performance Qualification (PQ) – demonstrates that equipment consistently continues to perform according to a specification appropriate for its routine use. Where possible, traceable calibration and verification tools should be used. Appropriate actions may include:

- Combination of method-specific calibration checks and SSTs.
- Regular, planned non-method-specific checks (*e.g.* 12-month intervals).

- *Ad hoc* checks (e.g. following repair, changes, modification and movement).
- Use data (especially SSTs) to evaluate trends and anticipate problems.

**21.7.3.7 Methods Validation.** Analytical methods used for the testing of drug substances and medicinal drug products should be validated. Validation should comply with ICH guidelines and involve assessment of the following main characteristics or elements:

- Specificity
- Accuracy
- Precision–repeatability–intermediate precision
- Limit of detection
- Limit of quantitation
- Linearity of assay
- Range of assay

In addition, assessment of some other elements may be useful, for example:

- Linearity of detector response
- Precision of sample introduction/injection
- Stability of sample and standard solutions

Robustness, the effect of small but deliberate variations in method parameters, should be assessed during validation if not already examined during the method development process. Information gathered during robustness assessment is a key factor in establishing system-suitability tests and criteria for an analytical method.

Reproducibility, *i.e.* precision as measured between laboratories, should also be assessed if and when it becomes necessary to transfer a method to other laboratories, whether within a company or to other companies or organisations. Reproducibility must be determined for standardised methodology or methodology proposed for compendia.

For some types of testing, there may be a requirement and/or it may be prudent to evaluate or confirm other characteristics as part of the validation process. For example, with dissolution tests it may be appropriate to confirm that sink conditions are achieved and to examine intra-pot and inter-pot variability (precision).

The extent and content of validation will vary according to several factors, primarily; the specification requirements of the material being the tested; the technique to be validated; and the stage of the drug product's development life cycle.

Figure 2 indicates which elements should generally be applied to different types of methodology.

Analytical methods for use in batch release testing of licensed medicinal products must be fully validated. However, at earlier stages of development, it may not be necessary or feasible to fully validate analytical methods, since there are several factors which will change during development, such as the synthetic route, the formulation (indeed, formulations for early clinical trials may be quite different to the eventual marketed formulation), product strength, packaging, knowledge of the compound and availability of well-characterised reference material. As a result, the elements required for validation may be phased, as indicated in Figure 3.

As discussed above, once a method has been validated, it is important to identify and control changes to the methodology or the materials to which it is applied, as any such changes may require re-validation of an affected method. Examples of changes which may require re-validation are different synthetic route for a drug substance, changes in formulation of a medicinal drug product and changes to the analytical procedure itself.



Application of Validation Elements

Validation Element	Type of Methodology			
	Identification	Impurities Quantitative		Assay
		Quantitative	Limit test	
Accuracy	–	+	–	+
Precision				
- repeatability	–	+	–	+
- intermediate precision	–	+	–	+
Specificity	+	+	+	+
Limit of detection	–	–	+	–
Limit of Quantitation	–	+	–	–
Linearity of assay	–	+	–	+
Range of assay	–	+	–	+

+ Characteristic applicable  
 – Characteristic not applicable

Figure 2 Application of validation elements

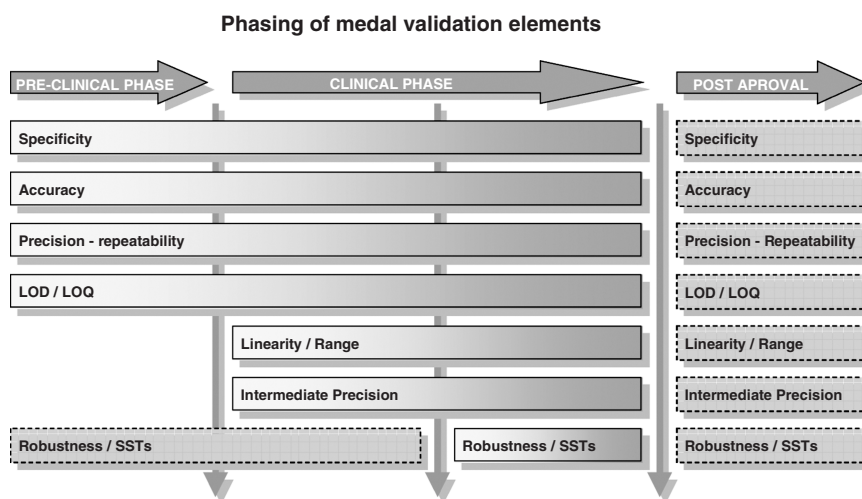


Figure 3 Phasing of method validation elements

**21.7.3.8 OOS/OOT Procedures.** Once all of the specification, testing, qualification, validation and change control systems have been put in place and are in balance in a GMP environment, wide variations in the results of chemical analytical testing would not be expected. Therefore, when a result is obtained which is OOS or in some other way unusual (OOT), the result and its cause must be investigated rigorously and, if necessary, corrective and preventative measures taken. This is discussed in more detail in Chapter 30.



This situation differs significantly from that in a GLP environment where the work is usually performed during the pre-clinical and early clinical development of a drug product. At that time, less is known about the materials under test, procedures and processes are developmental and under less control and many of the systems under investigation are biological with greater inherent variability. Therefore, unusual results may be expected from time to time and, in recognition of this, procedures may contain predetermined re-testing and acceptance criteria to handle such occurrences without resort to major investigation.

OOS and OOT results may occur in many types of testing in the GMP environment and it makes good scientific and business sense to investigate all such occurrences. Notably, however, formal investigation should apply to instances of OOS and OOT results occurring during batch release testing, stability studies and in the course of validation of manufacturing processes, cleaning procedures and analytical methods.

While all regulatory authorities would expect that companies establish written procedures for dealing with OOS and OOT results, the major influence on these procedures has been the US FDA, which has issued specific guidance on the subject. This requires that a procedure is established for handling of OOS and OOT results and it describes specific requirements of that procedure. This has a significant impact on the work of the analytical laboratory, since it is here that OOS and OOT results are identified and the analytical laboratory plays a key role in associated investigations.

The procedure for handling OOS/OOT results should describe the responsibilities of personnel in relation to investigation of OOS/OOT results, the framework and timeframes for investigations, the records to be maintained, re-test and re-sampling criteria and procedures and, importantly, it should define the point at which an investigation must end and a conclusion must be drawn. A log of OOS/OOT results should be maintained to facilitate trending and review.

The FDA guidance provides specific instructions with regard to some practices which are deemed unacceptable when investigating OOS/OOT results. The aim of these is to avoid situations in which batches are tested or sampled repeatedly until a passing result is obtained or until weight of passing results overcomes failing results through averaging the data. In brief, re-testing or re-sampling a batch may not be used as the sole means of overcoming an OOS/OOT result (unless indicated by a compendium, *e.g.* dissolution testing). Substantive, supportive proof of analytical or sampling error is required. Averaging OOS/OOT results with passing results or using outlier tests to discard OOS/OOT results may not be used as the sole means of addressing OOS/OOT results, especially where the testing is concerned with assessing variability, *e.g.* uniformity of content. In addition, the guidance emphasises the importance of expanding OOS/OOT investigations to evaluate any potential wider impact of the results and associated errors.

When an OOS/OOT result is obtained during the course of testing, an investigation must ensue. The aim of the investigation is to reveal the cause of the OOS/OOT result and to evaluate the impact of the result and the error which led to it. Such an investigation must be conducted in a timely manner, by appropriately authorised personnel and with accurate and chronological records of events. In general, investigation of an OOS/OOT result should be completed within 30 business days of the result occurring.

There are three categories into which the cause of an OOS/OOT result may fall; laboratory error; non-process related (operator) error; and process-related (manufacturing) error. In this context, the word “error” covers a wide range of problems that might occur during the manufacture and testing of samples.

Laboratory error covers OOS/OOT results which are caused by events such as laboratory-equipment malfunction (which may result in failure of SSTs to meet acceptance criteria), unrepresentative or mis-handled samples and mistakes made by laboratory analysts in conducting the testing.

Examples of the causes of non-process related errors are manufacturing equipment malfunction, accidental contamination during manufacture and mistakes by manufacturing operators during production.

Process-related errors are the result of the failure of the manufacturing process itself and indicate that the process is not robust and under control, for example reaction temperatures and drying times which do not always achieve the desired result.

When an investigation positively identifies and provides evidence for a laboratory error, the OOS/OOT result may be discarded and the test repeated to provide a replacement result. In some cases, laboratory errors may be easily identified through the review of records or examination of equipment or samples. Such errors may be termed “obvious errors”. In other cases, it may be necessary to perform some investigative analysis or re-sampling in order to identify the cause of a laboratory error (see Table 4, Chapter 30). Such errors may be termed “hidden errors”. When a laboratory error is identified, it is good practice to conduct an impact assessment to identify any other batches, products or processes that could have been affected by the error and to propose corrective and preventative measures.

When an investigation confirms an OOS/OOT result, whether it has been caused by non-process or process-related error, the batch under test must be rejected and the investigation must be widened. The widened investigation is termed a “failure investigation” and its aim is to uncover the source of the error, to identify any other batches, products or processes that could have been affected by the error and to propose corrective and preventative measures.

A third possible outcome of an investigation is that it is inconclusive, *i.e.* the OOS/OOT result cannot be replicated or confirmed and no error or cause can be identified. In this case, the OOS/OOT result must be retained in the batch record and given full consideration in the decision as to whether or not the batch should be released or rejected. This situation is complicated and great care should be taken in arriving at a conclusion.

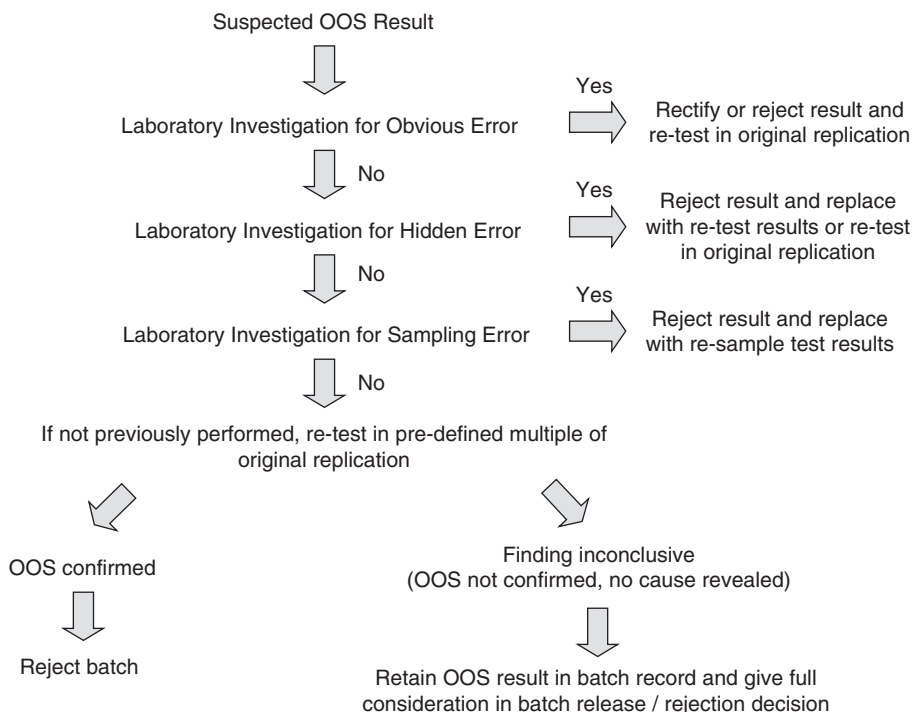
Figure 4 outlines a typical investigative process for OOS/OOT results.

The above discussion deals with the occurrence of occasional and isolated OOS/OOT results. In the event that multiple or recurrent OOS/OOT results are encountered, a much wider investigation and evaluation is warranted. Multiple or recurrent OOS/OOT results are indicative of a more serious problem in the laboratory and/or manufacturing areas.

**21.7.3.9 Self Inspection.** It is generally expected and, in some national regulations, required that a company will have a system in place to monitor the implementation and compliance with GMP, provide assurance that established procedures and methods are being followed correctly and propose corrective measures when necessary. A requirement of such a system is that it should be implemented in an independent manner. In general, this is achieved by establishing an auditing and inspection team, which reports to QA or company management. The team should inspect the various elements of GMP, including the self-inspection system itself, according to a pre-arranged plan.

**21.7.3.10 Archiving Periods.** GMP regulations require that records are retained for specified periods to facilitate their examination by regulatory authorities or by company personnel should the need arise, for example in the case of product complaints or recalls and pre-approval inspections. The records of the testing performed by the analytical (QC) laboratory are included in this requirement.

For licensed medicinal drug products, analytical laboratory records must be retained for a period of 1 year after the expiry date of the batch to which they relate. However, it should be noted that it may be required that some records and registers, such as those relating to OOS investigations and



**Figure 4** A typical OOS investigation process

product complaints and recalls, should be retained indefinitely or at least for the lifetime of the product.

For records associated with the development of drug products, covering aspects such as stability testing and methods validation, guidance on required retention periods should be sought from the relevant regulatory authority or published guidance.

## CHAPTER 22

# GLP in Drug Metabolism and Pharmacokinetics

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This chapter discusses three aspects of the application of GLP to drug metabolism and pharmacokinetics. Firstly, it provides an outline of the areas where the regulations apply; secondly, it discusses areas within these regulations that have given specific problems in their adaptation to drug metabolism and pharmacokinetic studies; and, finally, it mentions the practical applications of QA activities, with some indications of novel approaches to ensure compliance within the regulatory framework.

### 22.1 GLP REGULATIONS AFFECTING DRUG METABOLISM AND PHARMACOKINETICS

Drug metabolism and pharmacokinetic studies in animals are an essential part of the pre-clinical safety evaluation of a new drug or chemical substance, and are undertaken as a means of validating the animal species used in toxicology studies. It is within these confines that the general belief that it is essential to treat all studies, whether toxicological or drug metabolism, pharmacokinetic or analytical, as equal. The need then to apply good laboratory practice (GLP) to these areas of work becomes self-evident. Within the United Kingdom the regulatory inspectorate from the Department of Health has indicated that these studies are an essential part of the safety data, and that during inspections of laboratories drug metabolism and associated areas will be critically reviewed.

However, there is some conflict at the time of revising this chapter between the Committee for Proprietary Medicinal Products (CPMP) and the MCA GLP Monitoring Unit. The reader must be aware of the CPMP Note for Guidance (CPMP/EWP/QWP/1401/98) that became operational in January 2002. It relates to the investigation of Bioavailability and bioequivalence and, of particular importance, Section 3.4, indicates that analysis and validation should be carried out according to the GLP principles. Moreover, it further expands the GLP principles to be applied to the validation of the particular analytical method, something that has not been envisaged for many true GLP studies. The conflict arises whereby these analytical laboratories are required to be part of the monitoring programme and, therefore, do not readily agree to inspect these facilities. If reference is made to the appropriate directive, which initially sets out those studies required to be in compliance with GLP, it is quite clear that the discipline described above does not fall within that remit and, therefore, technically, the MHRA GLP Monitoring Unit is quite right in their interpretation. It does, however, cause a problem for those laboratories and, those sponsors who wish to adhere to the letter of the law; in that, technically, samples from these studies are required to be assayed in a GLP laboratory, or a laboratory operating to the principles of GLP. The Catch 22 situation comes when these laboratories cannot be part of the compliance monitoring scheme.

It is still a matter for debate whether or not other European or American regulatory agencies will follow the same criteria. However, discussions with these regulatory bodies have shown that the trend is to look more deeply at 'safety' studies with regard to their compliance with the principles, guidelines or regulations of GLP currently in force within each country.

## 22.2 TOXICOKINETICS

Although the US Food and Drug Administration (FDA), the Organization for Economic Co-operation and Development (OECD), and the VI Amendment EC Regulation 79/831/EEC, do not directly place drug metabolism and pharmacokinetics under a GLP requirement, as outlined above, the UK and OECD Safety Testing Schedules do refer to animal studies in these areas as 'toxicokinetics', which is defined as the study of the absorption, distribution, metabolism and excretion (ADME) of test substances. The EC is currently considering a new text for OECD guidelines in this field. The current EC view is that 'toxicokinetics' experiments should be performed only when essential from a toxicological viewpoint. The various regulations, however, do discuss 'toxicokinetics' in a similar manner to toxicological studies, and imply the need for their compliance with GLP.

## 22.3 SAFETY STUDIES

An area that has for many years promoted much discussion, and continues to do so, is that of good clinical practice (GCP). Encompassed within these regulations, guidelines and principles, are the FDA Bioavailability and Bioequivalence Guidelines within the Biopharmaceutical Compliance Program. The application of kinetic and metabolic studies to define safe usage of human drugs includes bioavailability, multiple dosing and interactions with other drugs. These studies may be performed in humans, and call for extensive analytical evaluation both of the parent drug and its metabolites. Studies such as those mentioned above are within the scope of GCP, the Bioavailability and Biopharmaceutical Guidelines and, therefore, compliance is necessary to achieve a successful new drug application (NDA).

Reference should be made to the earlier discussion on the CPMP bioavailability and GLP assays document.

It is the author's belief, therefore, that drug metabolism and pharmacokinetic studies should be placed under a regulatory umbrella of GLP. From a general requirement of the regulations, and more essentially from a moral viewpoint, it is necessary in certain instances to ensure that the marketing of compounds is carried out with the maximum of safety.

Therefore, it becomes necessary to review the GLP principles that were essentially established for use in toxicology, and 'interpret' these for work in other areas, particularly in drug metabolism and associated studies. Departments working under this code of practice usually deal with drug metabolism, pharmacokinetics and analytical and pharmaceutical developments. In many instances these departments are backed up by a radiochemistry laboratory, as work carried out includes the use of a radio-labelled compound. All areas are involved to a certain degree in GLP. Those laboratories not coming directly under the principles of GLP, such as clinical pharmacology and drug discovery, are advised to work to good scientific practice. In drug discovery the production of standard operating procedures, performance of regular instrument maintenance and calibration techniques, and raw data recording, should comply with the overall standards and principles of GLP.

The scope of metabolism work includes:

- (i) Quantitative ADME studies.
- (ii) Whole body autoradiography (WBA).
- (iii) Biliary excretion.

- (iv) Development of isolation, separatory (*e.g.* HPLC or GC) and spectral (*e.g.* MS or NMR) procedures.
- (v) Pharmacokinetic studies in animals (*i.e.* work on the kinetics of ADME processes of parent drug and/or major metabolites), including bioavailability studies.
- (vi) Toxicokinetic studies (*i.e.* the determination of drug levels in the plasma of animals during toxicology studies).

## 22.4 AREAS GIVING SPECIFIC PROBLEMS FOR GLP IMPLEMENTATION

### 22.4.1 Specific Problems Encountered

As has been stated, GLP regulations were drawn up to cover toxicology studies. Drug metabolism and pharmacokinetic studies differ significantly from normal toxicological studies in several aspects. They are concerned with animal studies that are open-ended, without the clearly defined time span of a toxicology study, which has a definite start and finish date.

Radioactive materials, which are inherently unstable due to radio decay, may be available in too small a quantity to permit normal chemical purity testing.

The complex instrumentation used in the performance of drug metabolism, or pharmacokinetic studies and their associated analytical technique, requires specific calibration, maintenance and quality control procedures to be set up.

The drug substance itself may well be destroyed in a study and thus pose the secondary problem of not being able to retain samples.

In the animal species used for drug metabolism and pharmacokinetics, there is often little difference between that of a toxicological study and thus poses a problem for 'justification of the test species'.

### 22.4.2 Attempts to Resolve the Problems

In view of the problems outlined, a philosophy of GLP in terms of quality standards should be applied to drug metabolism and pharmacokinetics. Certain areas of work may require 'a thought process' to ensure regulatory compliance.

The following examples demonstrate the range and variety of difficulties that can be encountered and give an indication of how good management techniques, good science and GLP can coexist in harmony.

## 22.5 PROTOCOLS

ADME are not routine procedures, unlike mainstream toxicology and, therefore, protocols may vary extensively from experiment to experiment. It may be that until the conclusion of one piece of work, one cannot draw up a protocol for the next. Hence it is difficult to comply with the current regulatory requirement for detailed protocols. For example, in metabolite isolation a completion date is extremely difficult to predict. Likewise the start date is entirely dependent on the production of radiolabelled material. The date the protocol is supplied and signed by the sponsor also poses a problem. Often contract research companies carrying out studies on behalf of sponsors, submit a protocol duly signed by their staff, but would not necessarily expect to get the sponsor's signature on the final definitive protocol until some time later. Usually verbal agreement is given, a letter of confirmation sent and, once the radiolabelled material is available, the protocol goes forward for final sponsor's signature and the study starts.

Another area of 'non-compliance' surrounds the justification for selection of the test system. In most cases drug metabolism studies identify the likely species for toxicological work. The ADME



studies tend to use rodents and dogs, and, as such, it is very difficult to give additional justification for the selection of these animals. However, with due consideration to the science and the objectives, some justification can be given.

In performing ADME studies to GLP principles, certain areas may be termed 'grey' with regard to compliance. In order not to contravene the regulations, it is necessary to indicate the problem and how this has been resolved in the most compliant and cost-effective way. Policy documents outlining this approach should be drawn up. These documents can outline what initially appear to be points of non-compliance, with reasons why the aspects of the principles of GLP cannot be fully met. This approach has the approval of several regulatory bodies. Obviously the production of these policy documents should not be seen as the means to avoid the compliance programme, and attempts to ensure compliance should be maximised.

## 22.6 DRUG SUBSTANCE

It is not always possible to control the drug substance strictly according to the GLP principles. Thus the small quantities of radiolabelled material used in drug metabolism studies make it impractical to carry out the chemical identity and pharmaceutical related tests that are applied to the bulk substance used in toxicology studies. Nevertheless samples should be formulated, according to principles of good manufacturing practice, in the pharmaceuticals group, and according to GLP principles and regulations within the company's test compound control area. In most instances this area would be within the formulation or pharmaceutical development section. The test compound control (TCC) would carry out the quarantine-type testing and release procedures for the testing and verification of non-radiolabelled material. In TCC all operations would be detailed in SOPs, records of drugs dispensed being maintained with strict accountability records and formulation reports produced.

Regarding radiolabelled material, regular tests for purity (chemical and radiochemical), and strict procedures are observed, with raw data records and SOPs being produced. Specifications should be set for acceptable purity before an experiment is started. Material outside this specification should be rejected for resynthesis or repurification.

In the case of non-radio-labelled test substances a reserve sample of approximately 1 g should be stored for 5–10 years in accordance with GLP principles and regulations, or for as long as the substance affords valid or valuable scientific evaluation. In the case of radiolabelled test substance, radio-composition makes it impractical to store reserve samples over such a period, and test sample retention is usually impractical.

## 22.7 SAMPLE RETENTION

In many drug analyses in biological fluids the analytical method leads to the destruction of the sample, through derivatisation for gas-liquid chromatography, for example. Drug metabolites may be extracted from thin layer chromatographic plates for analysis, and, again, these would be destroyed in their identification processes.

The storage of radiolabelled material arising from samples produced during metabolism studies may also not be available for retention. In drug metabolism studies or tissue distribution experiments many tissue samples are destroyed during the combustion process regularly employed before radiochemical counting. WBA experiments are often run in parallel with these types of studies, and the microtome sections from these experiments are retained. This again poses a problem in the archiving of such data. Each test site within the United Kingdom and Europe would be allowed to maintain stocks of radiochemical material up to a certain level of total radioactivity. This would limit the number of slides, *etc.* possible to be stored. Obviously with the increased retention period for the WBA microtome slices, the amount of radioactivity will increase as more and more tissue



slices are retained. Archiving of these materials would also pose occupational health and safety problems, and require the area within the archival facility to be designated as containing radioactive material and marked and treated accordingly.

## 22.8 ANIMALS

Whereas 100–200 animals could be utilised to obtain a statistically valid result in a standard toxicology study, in ADME and pharmacokinetic studies as few as three animals may be used for metabolite identification. Results may be qualitative but may not be statistically sound. A second area is with regard to sex differences. Thus equal numbers of male and female animals are always used in toxicology, but not necessarily in ADME work. This trend is in keeping with the ethical desire to reduce the use of animals in research.

The unique identification of animals is essential and obligatory. In many drug metabolism studies the dog is used for more than one experiment. It is, therefore, essential that each animal's record shows that no residual effect or material is present in its body before re-using the animal for the next study, and that it has had a minimum rest period of 1 month. Again on a purely practical note, it is essential that regular attention is paid to the ear-marking tattoos, as these, over a period of years, tend to fade and need renewing. One novel identification aspect that has been carried out in certain companies is to photograph the dogs and place an identity photograph on each cage and record card. In many instances the dogs used for experimental purposes – beagles – have sufficiently different markings to make each one easily identifiable, and they may well remain on study for up to 7 years.

However, under Home Office legislation in the United Kingdom, the re-use of animals conditions must be strictly followed and it is up to each individual practicing scientist to liaise with the animal unit and to ensure that the regulations governing the multiple use of animals is in accordance with the Home Office or other local country regulation and that their Home Office license or other country license, allows them to carry this type of activity.

While dealing with animals in general, we should not overlook the fact that the two legged animal, the human and principal investigator, also form a very important part of many bioavailability and bioequivalence studies, carried out in Phase I units in the clinical arena. While the earlier comments on housing and identification do not immediately apply to these creatures, there must be a full accountability and welfare issue to ensure that the healthy volunteer and subsequently the patient is correctly treated, most importantly that their identification are protected under the EU data protection directives. This is especially important when samples are taken from the clinic and sent to analytical laboratories for assays for PK. The whole aspect of dealing with volunteers and patients is further addressed in the chapters covering clinical trials and Phase I units.

## 22.9 RAW DATA

In certain departments a large number of compounds may be worked on at any one time, and it would not be practical to have a separate notebook for each compound, or to use loose-leaf records. In the interests of economy, and to ensure that each scientist or technician records raw data according to the principles of GLP, proforma sheets that are eventually bound into notebook, or single laboratory notebooks issued to an individual, can be instituted. Each notebook could, on the spine, have a unique coding, giving the initials of the owner and the date the notebook was issued. All notebooks should be returned to archives upon completion and the next consecutive number allocated to the new notebook. In this environment, all staff would have their initials and department recorded on computer file to ensure no duplication occurs. All instrument printouts, thin layer autoradiographs, *etc.* can then be either bound into the book or contained in a separate file bearing the same coding and cross-referenced to the original notebook.

Although each notebook is personalised, this does not negate the requirement for signatures of the scientist or technician, the next in the line management structure and the study director. As an aspect of QA inspections during facilities audits, the location and status of each notebook can be checked by quality assurance and cross-referenced to the archival record.

Raw data may be held as working records in the laboratory for some time, and thus their dispatch to archives delayed. For example, chromatographic traces and reference material may need to be referred to during current or related studies. To cater for this, one should establish departmental archives, which are regularly inspected by QA and the archivist to ensure compliance with all aspects of GLP. The contents of these departmental archives should be sent to the main archives as soon as they are no longer required.

## 22.10 PRACTICAL IMPLEMENTATIONS OF GLP

Attention must be paid to electronic data and their transference. References must be made to FDA under their CFR Part 11, Electronic Signatures and Data Rule. The movement of these materials and compliance with this guideline is very important when submitting data to registration authorities in the United States. Over the past few years, however, we have seen quite a change in the implementation and requirements of CFR Part 11 and most recently, February 2005 saw some reviews and down-grading of this activity. In general, as can be seen from references to other chapters on computing in this book, provided that the predicate rules are followed, then adherence to Part 11 is almost guaranteed.

This section reviews in more detail other problems associated with principles of GLP compliance, such as: standard operating procedures, maintenance and calibration procedures, computer activities, protocol, experimental and report auditing and ancillary quality assurance activities.

## 22.11 STANDARD OPERATING PROCEDURES

Standard operating procedures must be produced for all aspects of work.

The term 'metabolism' often covers all studies of the fate of xenobiotics (foreign substances) in animals and man. For the purpose of this chapter a narrower definition covering the fate of chemical substances in animals will be used, to include the associated analytical techniques, but excluding metabolism and pharmacokinetic studies in human volunteers and patients.

The earlier stages of a programme of metabolism work, such as research support aiming at selection of a lead compound, are likely to be purely exploratory in nature. The intermediate phases, such as Phase I work for the registration dossier, and the final stages, such as Phase II and III (post-CTX certificate), which may include the repetition of some of the work under more precisely stated conditions, will be scrutinised most closely by regulatory authorities.

All the studies detailed earlier in this chapter would be the subject of extensive SOPs. These SOPs would cover in detail the experimental design and operation of these studies.

There is very little difference between the process of production, distribution, updating and archiving drug metabolism SOPs and those for toxicological studies. Suffice it to say that a system should ensure indexing, recording and issuing, and that all parties work from the most current SOP, issued from a central system covering the appropriate activities (see Chapter 16).

Having outlined the specific studies that would require SOPs, we may find it worth while looking at more specific areas within ADME, and itemising these into an experimental sequence, to give an overview of those ADME procedures requiring SOPs. Examples include:

- (i) Protocol production
- (ii) Release and monitoring of test substance
- (iii) Animal treatment with radioactive substance
- (iv) Specific data recording and its storage problems

- (v) Storage of samples subject to radioactive decay
- (vi) Operation of equipment
- (vii) Use and husbandry of experimental animals
- (viii) Experimental procedures
- (ix) Disposal of samples
- (x) Data-recording
- (xi) Report production
- (xii) Quality Assurance Unit procedures.

This is not an exhaustive listing, and there may well be additional areas subject to the production of SOPs.

## 22.12 TYPES OF DOCUMENTATION USED FOR SOPs

There are three common types of documentation which function as SOPs:

- (i) *Research papers/reports*. With the ever-increasing amount of research required in metabolism studies, it is not uncommon to see a reprint of a method taken as an SOP.
- (ii) *Manuals*. Where manufacturers' instrument manuals are not over-complex, they can be used in total for the operation procedure. However, in some instances a précis of the relevant points would seem more appropriate. In either case strict instructions must be given for the company's procedure for routine/non-routine repair, to avoid giving carte blanche to 'screwdriver operatives' to use the manual to dismantle a machine.
- (iii) *Conventional SOPs*. The third area of SOP documentation would be that recognised as a standard document.

In looking at the type of documentation the three words themselves in isolation should be reviewed:

- Standard – to whom?
- Operating – effectively and with associated staff knowledge.
- Procedures – rigidity, vagueness or completeness.

Two specific areas where problems may be encountered are worthy of mention: analytical procedures are becoming very 'high-tech', making the checking and adherence to SOPs very difficult. Likewise, developmental work cannot be tied to a rigid procedure, and thus in itself will be the basis for a draft SOP, culminating in a final SOP once the method becomes routine. Radio-immunoassay (RIA) techniques are becoming more frequent in their usage for 'one-off analyses'. The manufacturer's instructions are, therefore, the basis for the SOP content. Quality assurance, therefore, should ensure a copy is lodged on file as, or in lieu of, an actual SOP.

In drug metabolism SOPs should be written to make allowances for different isotopic labels, especially in counting combustion procedures. Differing storage times may also result from varying isotopes. Similarly, SOPs should be written to allow for variance of animal strain, throughout a series of studies.

## 22.13 EQUIPMENT MAINTENANCE AND CALIBRATION

The FDA GLPs (Section 58.63) and OECD GLPs (Section 4.1.2), along with all current GLP principles produced within countries, specify a similar procedure to adopt when implementing a maintenance and calibration system. Most of the equipment utilised in today's laboratory is becoming increasingly complex and specialised compared to the average equipment used in a standard toxicology study.

In general, there is very little difference seen between the equipment maintenance and calibration procedures of a toxicology study versus that of an ADME study. Common practice is for the section responsible for the equipment to record the receipt on a card index or computer, and provide service contracts and routine or non-routine servicing.

#### **22.14 EQUIPMENT MAINTENANCE AND CALIBRATION WITHIN DRUG METABOLISM**

In general, an ADME laboratory would have a variety of instruments, ranging from pH meters, balances, spectrophotometers and TLC scanners to complex combustion and radiochemical detection equipment. TLC plate scanners and HPLC equipment require daily calibration with reference to analytical standards produced for the particular assay in question. The purity of the radiolabelled compound is of paramount importance, as is the purity of the market standards, so that regular calibration of the instruments and procedures is again required.

In most laboratories a service department is responsible for the maintenance and calibration of liquid scintillation counters and oxidisers. Routine instrument calibration should be carried out regularly to ensure the satisfactory working of machine and materials. Should any form of electrical breakdown occur, or erroneous results be shown up, this procedure should be repeated more frequently. The recording of all calibrations must be kept in the counting services area, along with a record log for machine faults and their rectification. In addition to regular routine calibration, daily quality control checks should be carried out, using a system of 'spiking' or internal standardisation. For each tray or group of trays, after a run has been passed through the machine, a sample should be taken at random and the efficiency be measured again. This is usually carried out with the addition of an internal standard. These values should be entered on to the results sheet and used as a guide as to the performance of the system.

Service contracts should be taken out for all major pieces of equipment when this can be justified on a cost-benefit basis.

#### **22.15 WHOLE BODY AUTORADIOGRAPHY (WBA) EQUIPMENT**

Freeze driers and cryostats are the main instruments, and require attention for their correct and effective use. SOPs should be produced for each piece of equipment, and a maintenance section contained in each document. Calibration should cover the X-ray film and histological section thickness. Random checks should be carried out on the microtome to check for section thickness, in addition to daily visual appraisals. For example, evaluation of new X-ray film requires the use of standard calibration tests (a step density ladder using carbon-14 glucose standards). All operations should be recorded in the laboratory notebook with correct signature.

In the photographic section, maintenance should be restricted to the enlarger, camera and print processor. Safe-light-filter checks should be carried out routinely, and provided these prove satisfactory, no action is required. However, should a filter fail the check, it should be discarded and replaced, labelled with the date of installation, and records made in the photographic section log. Chemical solutions for print processor, developer and histological stains should be labelled according to the GLPs, as the total quality of the print in this area directly reflects the 'raw data'.

#### **22.16 COMPUTING EQUIPMENT**

Computers are used to record receipt, transcription and calculation of data generated elsewhere in the laboratories.

Like any other piece of equipment, they should be covered by regular maintenance contracts, and all records of routine or non-routine maintenance held within the department. As problems occur,

details must be entered into the instrument log and, upon completion of the repair, appropriate details should be entered by the computer engineer into the system support log.

Special reference should be paid to the chapter on computers and validation paying particular attention to CFR Part 11 of the FDA.

## 22.17 DATA GENERATION AND SECURITY

As with any toxicology study, large amounts of data analyses will be carried out via a computer. In some areas machines, such as liquid scintillation counters, will be coupled on-line to the computer, while in others, such as pharmacokinetic areas, the data are entered manually and manipulated by various software programmes.

An emphasis is placed on curve fitting, the data entries must be validated by another technician and then by the computer programme itself. Much interest is now being directed at the GLP implication of data capture and manipulation by computer or computerised systems, with special emphasis being placed on file security (see Chapter 37).

For liquid scintillation counting special security systems should ensure that all data generated and transferred to the computer are copied as the archive version, to prevent tampering. Most counters nowadays will have a multiplexer data store, where data are held until the computer is available. On demand from the computer these data are released and automatically date- and time-stamped. The first security check should be to ensure no person has access to the clock. It is further suggested that each file is then given a security code, which is generated by a separate computer programme relating to the tray containing the samples for initial analysis. On the printout or visual display unit the beta or gamma counter number and the information relating to the particular experiment are given. Duplicate copies, as already stated, will be held in a computer archive, and should editing be required, the original file would be date-stamped to show re-entry.

As with all computer operations, strict security, validation of raw data and signing procedures should be seen to comply with GLP principles exactly as outlined in a toxicology study. Further reference to QA considerations of computerisation is given in Chapter 37.

## 22.18 EXPERIMENTAL ACTIVITIES

Following on from equipment, its maintenance and calibration, comes the experimental phase. As has previously been outlined, there are many studies comprising ADME. With regard to experiments and inspections, there is no difference in the QA approach to identifying critical phases for drug metabolism studies to that of toxicology studies. In effect, this critical phase distinction may be simpler, in that the protocol, experimental and report stage would be considered critical within ADME. Each phase should have at least one inspection. As with all QA activities, those within the confines of drug metabolism are no different. Master scheduling indexes would be set up, and standard operating procedures produced for planning and performing inspections, the identification of critical phases, reporting to study management and report auditing.

## 22.19 PROTOCOL INSPECTION

The objectives of a given metabolism study may be defined in the protocol at the outset, but the route by which they are to be attained may need to be defined and perhaps redefined as the work proceeds. This is in contrast to the situation with most toxicology studies, in which very precisely detailed protocols can be written. As the result, the QAU may need to plan certain of its activities progressively for metabolism studies as the work proceeds, in order to include the techniques, procedures and equipment which are found to be necessary. The monitoring of the practical work may be performed on a study or a procedure basis, or a combination of these.

Whether the QAU should review all ADME protocols is a management decision. Just as preliminary 'research toxicology' study protocols do not have to be reviewed for GLP compliance, so preliminary ADME study protocols may not always be audited by QA. It is important in this case to define precisely those types of study for which a GLP compliance review is required, so that confusion does not arise over what is or is not to be a GLP-monitored study and cause the laboratory to operate to dual standards.

It has been claimed that it is impossible to design a protocol for a metabolism study, since a study's objectives could not easily be defined and the experimental design procedures described would be too vague to be meaningful. The foregoing prove this stance to be unfounded, and in general the agreement should be that it is possible to produce as comprehensive a protocol for a metabolism study as for a toxicology study. Items required for a GLP study protocol and their applicability to metabolism include the following.

*Study objectives:* These should be stated as clearly as possible, as for toxicity studies. A clear declaration of study objectives determines whether the study will be the subject of a QA review.

*Test and control items:* Little difference exists between toxicology and ADME, apart from the already mentioned problem of radiolabelled material.

*Dose formulation and administration:* Unambiguous instructions should be included, a factor of particular importance when administering a mixture of initially radiolabelled and non-radiolabelled materials.

*Test system:* ADME studies used to support toxicology studies must essentially use the same species or test system. For full interpretation it is also important that some selection criteria be used with regard to the age and sex of the animal, and the route of administration, which should also match that used in toxicity testing. For ADME studies performed on animal test systems, consideration should also be given to possibilities of variability in diets affecting interpretation of the results and feeding/fasting cycles. Where the test system is not an animal species, but, for example, a soil type, then the selection for justification will be different. An example would be 'the soil type(s) used in this study are those expected to be exposed to the test article in the environment and the method of application is that recommended by the regulatory authorities'.

## 22.20 TYPES OF MEASUREMENT AND FREQUENCY OF OBSERVATIONS

Here, little if any, difference between the two types of protocol exists. Other aspects, such as starting and finishing dates, sponsors, testing guidelines, records to be maintained, dates of agreement and signatures of managers and study directors, along with methods of determining degrees of absorption and responsible personnel, differ very little between drug metabolism and toxicology studies, and in total should all be included in the standard protocol.

## 22.21 EXPERIMENTAL INSPECTION AND RAW-DATA AUDITS

Experimental inspections, although somewhat routine, should not be solely checked by means of a checklist. A standard checklist gives a certain number of headings, but it remains paramount that the inspector use these and other factors observed as the experiment progresses to ensure compliance. It is an essential aspect in drug metabolism, and in toxicology, that intermediate in-life raw-data inspections be carried out regularly. It is normal to schedule an inspection 1 month after the start of the study to ensure that all aspects are proceeding well, and an intermediate inspection, plus one before the study is terminated. This schedule will, however, change with study types, especially very short-term studies.



## 22.22 REPORT INSPECTION

As with all GLP studies, ADME experimental work culminates in the production of a report which should be sent to QA for audit before distribution. Each report should be inspected initially in isolation, and then with reference to the raw data, which itself should be audited for completeness. Unlike reports from toxicology studies, most drug metabolism reports need to be inspected in total, since they do not lend themselves to random selection procedures or statistical appraisals, such as outlined by British Standards 6001 (see Chapter 32). It is standard practice for QA to inspect tables and figures, have to perform random recalculations, and then ensure that correlation between tables and text, results and tables, discussion, summary and results, accurately reflects the raw data and comes within report compatibility.

## 22.23 REPORTING TO STUDY MANAGEMENT

Following inspections, inspection reports should be produced for study management, even if all operations are considered to be in compliance, so that quality assurance can demonstrate that a satisfactory inspection has been carried out. As with any GLP study, it is emphasised that study audit reports are confidential. Adequate communication is essential to ensure the agreement of all parties is obtained on the non-compliance points identified.

## 22.24 CONCLUSION

This chapter identified the areas in which the regulations apply. Areas causing specific problems in the adaptation of drug metabolism and pharmacokinetics to the GLP principles, guidelines and regulations currently in force have been discussed, and approaches to assure compliance proposed. With the current review of regulatory attitudes, *e.g.* towards computerisation and GCP, it is the author's belief that very shortly all aspects of safety studies will fall under the umbrella of GLP, and any aspect of a safety study could be reviewed to achieve compliance status.

While the GCP and good manufacturing practices have been revised dramatically since the first edition of this book, GLP really has not moved on too far. Within the 1997 revision of the OECD principles of GLP, no move was made to incorporate drug metabolism or pharmacokinetics into the GLP system.

Since the inception of GLP, in 1976, it has been very noticeable that the American authorities have really not moved to embrace these two disciplines into their GLP.

However, within Japan, Europe and most importantly, the industry in general, there has been an agreement that the studies of drug metabolism and associated PK would be conducted as a safety study, in compliance with GLP.

Since 1980, many companies have voluntarily put their units up for inspection and, many companies have their units certified as operating in compliance with OECD principals of GLP.





## CHAPTER 23

# Issues of Quality in Pathology

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### 23.1 INTRODUCTION

To monitor pathology procedures adequately it is necessary to understand the process whereby samples of body fluids or other tissues are provided for analysis during life and at the terminal procedures when the animal is sacrificed and sent for detailed *post mortem* examination followed by histopathological evaluation and reporting.

Quality Assurance (QA) inspectors with no formal training or experience in toxicological pathology can only satisfactorily inspect some of the processes involved in toxicology studies. QA of other aspects of pathology can only be undertaken by an experienced toxicological pathologist in the form of peer review. Impractical as this may appear, peer review is commonplace in the modern era.

#### 23.1.1 Organisation

There are numerous distinct tasks within the area of pathological evaluation that may be divided within the laboratory's organisational structure. Pathology departments often comprise separate functional units concerned with one or more of the following functions:

- Clinical chemistry
- Haematology
- Necropsy
- Histology
- Histopathology
- Electron microscopy and other specialised techniques.

For logistical reasons the company management may place some of these units outside direct management by pathologists or combine one or more functions in a particular unit. Whatever the organisation, the generation of any scientific data must always be under the control of suitably qualified staff.

As most areas of pathology, apart from necropsy and histopathology that generate objective data, the processes and procedures employed in the generation of samples and results are accessible for inspection by QA inspectors with no specific pathology training.

### 23.1.2 Identification of Samples

The identification and tracking of samples (or animals) through the laboratory is of primary importance and must be carefully controlled and documented. Sub-cutaneous transponders can be inserted to provide unique identification of the live animal but this information must be transferred (often by hand) to a large number of samples during and after the live phase of a study. The transfer of information must be carefully controlled and monitored.

### 23.1.3 Equipment

In clinical chemistry, haematology and histology processing a wide range of high-tech equipment is employed. Any test used in the analysis of samples and generation of data must be conducted using the equipment that is fit for the purpose required, calibrated on a regular basis and maintained in good working order. As part of the process of calibration and validation, it may be necessary to generate a sub-set of control values at defined intervals and keep records of the exercise.

Processing equipment must be maintained according to a regular schedule and reagents obtained from reliable suppliers and stored appropriately. Faults in the processing of tissues can lead to a catastrophic loss of data.

### 23.1.4 Personnel

At all stages of a project, the final results depend on the calibre of the staff performing or supervising the various tasks. Just as equipment must be suitable for the purpose required, so must be the staff.

*23.1.4.1 Qualifications and Training.* The setting of academic standards and training programmes for each position requires judgement and regular review with some degree of guidance from regulatory agencies and relevant professional organisations. There are no easy solutions in this regard and it would be foolish to generate guidelines that are inflexible and potentially unworkable.

The demands of many jobs change quite frequently as a result of rapid advances in knowledge and technology. These changes must be taken into account in advanced training and continuing education programmes. An increasing number of professions recognise the need for 'lifelong learning' and employers should provide sufficient resources to enable the maintenance of up-to-date knowledge and skills.

A rising number of professions have developed continuing professional development (CPD) schemes that require the acquisition of educational credits on an annual basis. Eventually, these requirements will become compulsory for some professionals involved in GLP studies.

*23.1.4.2 Training Records.* Training records should be a positive statement of a person's development within a job rather than an empty process to satisfy a regulatory requirement. The record should contain sufficient details of the skills taught and the results of any assessment of competence acquired (Chapters 38, 39).

In professions where there is a formal CPD programme, the CPD portfolio could provide the bulk of the training record with regard to acquisition of new knowledge and maintenance of skills. Where there is no such scheme, the training record should accurately reflect the level of expertise that could reasonably be expected for a person in that position.

*23.1.4.3 Supervision.* Not all jobs could or should be undertaken alone. In GLP studies, checking and corroboration of key processes is essential for the integrity of the study. In jobs where experience can only be obtained over a long period, supervision must be provided to ensure that

mistakes are minimised as the learning process continues. This requires the allocation of sufficient human and physical resources as well as time in the work schedule.

## 23.2 STANDARD OPERATING PROCEDURES

As in other areas, procedures used in the conduct of the pathology phase of a study should be described in detail in a concise, understandable, easily accessed document. The SOP will gradually change over a period of time and current procedures must be kept up-to-date to accurately reflect the task that is actually undertaken rather than something that is idealised or out-of-date (Chapter 16).

Even those SOPs that do not seem to require revision must be reviewed by an appropriate person at regular intervals (at least every 2 years). As with training records, the document should reflect the actual tasks undertaken rather than satisfying a perceived regulatory requirement. If the SOP is not seen as a practical document by those that use it, something is amiss and it should be revised with some urgency.

As with all necessary manuals and guides, the relevant SOP should be easily available in the work place. New issues of SOP should also be read and understood by those required to use them and this process documented.

## 23.3 CLINICAL CHEMISTRY AND HAEMATOLOGY

Samples of body fluids (and other tissues/materials) from animals on test are commonly examined for a number of their constituents. This includes blood (serum and plasma), blood cells (haematology), bone marrow and urine as the most common routine samples, although other materials such as faeces, joint fluid, bile, broncho-alveolar lavage fluid, vaginal smears, cerebrospinal fluid, *etc.* may also be taken when required by the study plan.

Samples must be collected, preserved and stored appropriately if any subsequent tests are to be valid.

### 23.3.1 Collection

Collection of samples must be performed by trained individuals as incorrect technique can compromise the integrity of the sample. Contamination of samples should be kept to a minimum by the use of disposable equipment for collection from each animal and by adequate sealing of any container.

As an example of variability that can be experienced in the collection of samples, blood collection is used for the purpose of illustration. Blood may be collected from the limb veins or jugular vein in dogs or non-human primates. In rats, blood is taken from the tail veins or retro-orbital sinus in life and heart or vena cava during post mortem.

Samples from different sites yield slightly different results and comparisons must be made appropriately. In mouse studies, a separate group of animals is often allocated for collection in live samples. Excessively frequent or voluminous sampling can lead to effects on the health of the animals, which will be reflected in the values from subsequent bleeds.

The results of blood tests are also influenced by anaesthetics (if used) and the type of preservation used. Samples must be taken into plain glass containers and allowed to clot for serum samples, but unclotted samples require an anti-coagulant (*e.g.* heparin, CaEDTA, citrate, *etc.*) that is suitable for the subsequent tests to be performed. The samples may be subsequently centrifuged to allow the separation of cells and plasma.

Unless assays are to be carried out immediately, plasma samples are usually frozen for subsequent analysis. Refrigerators for their storage must have an uninterrupted power supply, alarms for out-of-range temperatures and records kept of their performance.

### 23.3.2 Analysis

The samples are generally examined using an array of tests that may be automated, semi-automated or manually operated. There is an impressive array of computer-controlled machinery that will conduct many assays on small samples of body fluids in large batches and in a reliable and reproducible manner.

It is essential that these machines are suitable for their purpose, calibrated for the species being tested, maintained appropriately (with documentation), tested before use and operated by trained, knowledgeable staff (also ensuring that accurate records of these procedures are kept).

There are many standardised, commercial assays for a wide range of commonly assessed components of blood and there are several commercial analysers that have been widely used in animal experimentation. A thorough understanding of the mechanism that underpins each test is required by the scientific supervisor, or else problems that arise may be difficult to resolve. A suitably trained and qualified clinical chemist should be employed whenever possible, especially in large departments. This will allow not only adequate supervision of sampling and analysis with suitable interpretation of the results generated, but also an informed approach to the development and implementation of new techniques.

Reagents for assays must be obtained from reputable suppliers with adequate safeguards of their quality and records of batch numbers and date of manufacture. New methods or reagents must be rigorously tested before use and records kept of the data used to verify their suitability. There are obvious potential problems when using test kits developed for use in other species.

Occasionally, manual tests must be used to measure parameters that cannot be assessed using commercially available kits. These test results are more prone to human error but may be as precise as automated assays if conducted with care by suitably trained and qualified staff.

## 23.4 NECROPSY

Necropsy procedures may involve the collection of the final set of *in vivo* data such as blood samples or urine and recording of body weight followed by the humane sacrifice of the animal and collection of tissues for further analysis. Final blood samples may also be taken after euthanasia, especially in rodents.

### 23.4.1 Organisation

The necropsy is an intense, critical phase of the study that produces a large mass of data and sampling, which cannot be reconstructed if mistakes are made. The safe and efficient conduct of the necropsy depends on a team of people working together. The study pathologist plays a critical role in the team that conducts the necropsy even though line management of this area may lie outside the pathology department. The pathologist should assume overall responsibility for the quality of the data generated and must work closely with the study director and technical staff to ensure that the objective of the procedure is met with.

Whether a prolonged necropsy procedure requires the continuous presence of the pathologist throughout is a moot point. In the terminal sacrifice of a toxicity study in rodents, the number of findings may be small and there can be long periods where the pathologist serves no useful function after the first or second hour. At this stage, many pathologists will be 'on call' rather than being continuously present, but this practice varies between companies. Some establishments insist on the continued presence of the pathologist, while others have more limited resources and deploy their staff differently.

The course of the necropsy can, to a great extent, be laid out in advance in the Study Plan and by a meeting of all parties involved prior to the scheduled sacrifice. The findings recorded during the course of the study, however, and some findings made at necropsy can lead to alterations in the requirements for tissue sampling. The pathologist may need to act quickly to ensure that vital data

is not lost and with the study director, can amend the Study Plan at the technical meeting or during the necropsy – in a hand-written form if necessary.

The technical aspects of sample collection can be undertaken by trained technicians, but necropsy findings should always be the responsibility of a trained pathologist, even though individual observations may be generated by experienced technical staff. In some respects, technical staff may be superior to pathologists in the dissection and collection of tissue samples as they practise these skills more regularly. A team leader should be identified to ensure that all tasks are completed satisfactorily and to take responsibility for the completion and signing off of the necropsy.

Training and supervision of staff are important factors in the necropsy and only suitably trained personnel should take part. The identification and correct preservation of samples (as well as health and safety) in an environment where numerous people are working in a relatively restricted space relies upon sensible planning of the necropsy room and management of staff.

Time, of course, is an important consideration and each necropsy must be completed before appreciable deterioration of the tissues takes place. The necropsy should take about 40 min or less (the quicker the better), but certainly not more than an hour, which means that the team conducting any necropsy must be capable of completing the task in the allotted time. Some organs degenerate quicker *post mortem* than others and the least vulnerable can be left until last. For instance, the gall bladder and intestines should be taken early on but the skeletal muscle and bone can be left until last. SOP should include an assessment of the time allowed for critical phases of the necropsy.

Important materials that should be present at the necropsy include the Study Plan and any amendments, relevant SOP, clinical record cards and equipment for photography as well as data-entry terminals or a suitable paper *pro forma*. Suitable equipment (including protective clothing) for conduct of the necropsy and suitably labelled containers of fixative are taken as given.

All tissues listed in the Study Plan must be sampled according to SOP or as detailed in the Study Plan. Usually a checklist is presented on the necropsy form with a space for the number of pieces taken and (if necessary) their storage location. It is usual for a supervisor to check that the correct number of tissues has been taken before the necropsy is officially completed.

The dimensions of samples for fixation are important as neutral buffered formalin (NBF) will not adequately penetrate more than 5-mm slices of dense tissues and thicker samples may not fix in the centre. The brain is fixed whole to harden because dissection of fresh tissue leads to significant damage and histological artefact.

Other samples may be required in addition to the standard list of tissues (*e.g.* frozen samples, samples for electron microscope (EM), bile) some of which may be in the Study Plan and others that must be taken in an *ad hoc* manner if an abnormality is detected. The judgement and experience of the study pathologist is usually required when reacting to unexpected findings.

Recording of necropsy data is often undertaken using paper records although suitable direct-entry computer programs are also available. Findings at necropsy may also be entered on to a computer system at a later date from hand-written records or tape recordings, although with added potential for transcription errors. A paper system must also be available in case of computer failure.

The *pro forma* or computer system must contain a checklist of required tissues and additional samples taken (including samples for EM or histochemistry) along with photographs and diagrams. Provision for the recording of necropsy findings, text comments, procedural variations and instructions to histology technicians should also be available. The data, whether hand-written or computer-based, must be checked and countersigned by a supervisor before the necropsy is considered complete.

### 23.4.2 Health and Safety

Adherence to the principles of health and safety of staff and animals must be assiduously observed. This is especially important with regard to protective clothing, use of toxic substances (fixatives,

anaesthetics), humane and safe handling of animals (especially potentially infectious non-human primates), use of sharp instruments and disposal of biological and hazardous materials.

Suitably trained personnel and established procedures must be available in case of accidents (*e.g.* first aid, incident and accident reports, consultation for specialist treatment and medical follow up of affected staff). Knowledge of potential zoonoses is essential along with the measures that are required to prevent potentially serious infections.

### 23.4.3 Storage

Correct storage of fixed tissues is important and some fixatives (*e.g.* Davidson's, Bouin's, Zenker's, Karnovsky's) require removal of tissues to other solutions to prevent excessive hardening and this need must be highlighted in the SOP of the necropsy and histology laboratory. Storage containers should be unbreakable and the labelling secure and legible under most conditions.

Storage areas must be secure, adequately ventilated and with a controlled temperature range. This is especially true for frozen tissues that must be kept at controlled temperatures in a safe area that is only accessible to suitably trained staff.

### 23.4.4 Organ Weights

The major organs of most animals are weighed at necropsy and these requirements are detailed in the Study Plan. Additional organs may be identified during the course of the necropsy that may need to be added to the list in the Study Plan and this eventuality should be provided for. Organ weights may also be made in an *ad hoc* manner in oncogenicity studies where organ weights are not routinely assessed as a guide to the degree of change in size.

Important features comply with the Study Plan, calibration of balances (with suitable records), accurate data collection (or record keeping), *i.e.* suitable computer program or *pro forma* and the correct identification of samples.

Many computer programs will highlight organ weights that fall outside a pre-defined range. These tissues will often need to be re-weighed to confirm the value. If this facility is not available, a similar manually operated system should be operated.

Organ weights can be made on fixed tissues, although they tend to be about 10% higher than fresh weights and so important data may not be completely lost if records are not (or cannot be) made at necropsy. An alternative to a computer-operated system must be available in case of unexpected computer/electrical failure during a necropsy.

### 23.4.5 Necropsy Findings

The findings should be the ultimate responsibility of the attending pathologist even though they may be recorded by the technical staff. In carcinogenicity studies, where there are many findings, it is impractical for the study pathologist to make all of the observations and trained technical staff members are capable of making reliable findings under supervision. As many laboratories use computer-operated data-collection systems, which offer a relatively limited glossary of standard terms, there is often a limited chance of inconsistent use of terminology.

The hand-written notes on the *pro forma* or the computer entry comprise the raw data for necropsy and must not be destroyed, obscured or over-written. Amendments must be signed and dated with a reason for the change while still leaving the original finding legible or available in the computerised audit trail.

Findings that are not recorded at necropsy cannot be reconstructed, and correlation with clinical records is an essential part of the procedure especially for the tracking of palpable masses and lesions noted in life. Clinical signs can be useful indicators of potential pathological lesions and



should be taken into account, especially in larger species (*e.g.* tremors, convulsions). These clinical records/summaries must be available to the prosector or pathologist at the time of necropsy.

In carcinogenicity studies, palpable masses must be accounted for, even if no corresponding lesion can be found and the identification and labelling of masses must be consistent throughout the study – mass A in life should not become mass 1 or mass B at necropsy.

Diagrams and photographs are useful adjuncts to the textual description of a lesion and must be prepared and stored in a standardised manner according to SOP. These materials must be readily accessible to the study pathologist/technician who should be trained in their use.

Care must be taken by the study pathologist to ensure that there is not too much variation in the recording of findings between different necropsy technicians. This means that some technicians may need more supervision than others in order to achieve consistency.

Inter-current deaths and pre-terminal sacrifices from studies may occur at weekends or at inconvenient times of day and a roster must be drawn up to provide trained staff and logistical support to perform such necropsies.

#### **23.4.6 Histology**

The fixed tissues from the necropsy laboratory are stored before being processed within the histology laboratory to provide histological sections for microscopic examination. Fixation is a relatively prolonged procedure and takes a week or more to complete and incomplete fixation results in serious artefacts (collapse of tissues in the block, loss of detail in sections) in the histological preparation of tissues. Tissues have hardened after about 24–48 h and can be trimmed but will need to be returned to fixative before processing. Even if the tissues are not trimmed, a change of fixative is beneficial.

Initially the samples of tissue are trimmed to a suitable size to fit into a histological processing cassette, which should be suitably (and indelibly) labelled. Tissue trimming should be standardised for each species to provide optimal and comparable samples of each organ as required by the Study Plan and the study pathologist. Extra samples may be required to include abnormalities described at necropsy and must be identified and processed accordingly.

Further macroscopic observations may be made during trimming and there must be a means for recording these findings for inclusion in the raw data and for the pathologist's information.

Trimmed tissues are then processed in a computer-controlled processor to replace water within cells with graded concentrations of alcohol to permit subsequent infiltration with paraffin wax. A failure in the processing cycle can lead to serious artefacts in the tissues and adequate maintenance programmes for the equipment are essential. In the event of failure, the use of replicates in the histology schedule will minimise the loss of data from one particular group of animals.

Processed tissues are usually embedded in the plastic cassettes that they were processed in and thus retain their identification. Embedded tissues are sectioned on a microtome, floated in a water bath and then affixed to labelled slides. Sections from each block must be removed from the water bath before a new block is sectioned. Sections of tissues from the wrong animal cannot be easily detected at a later stage.

The labelling of the slides may be temporary (in pencil, which is removed by frequent handling) or permanent (etched or printed on the slide) at this stage. Paper labels may be applied after staining but many laboratories have moved to the use of printed or etched slides. Mistakes at this stage, where the sections are applied to the wrong slide (or wrongly labelled), can be detected later by checking the block with the slide – although there is rarely a systematic check for this type of error.

Mounted sections are usually stained in batches in computer-controlled staining machines and the sections protected by cover slips, which may be applied manually or by machine. At this stage,

there will be a microscopic quality check of the slides by a technician and inadequate sections sent for re-cutting or re-sampling, *etc.* Samples that are sent back for further work must be documented while adequate samples will be countersigned on the *pro forma*/computer program and become available for collation.

Collation of the slides will include a check that all required sections (including macroscopic abnormalities) have been prepared and are of adequate quality or that any section that cannot be prepared is documented accordingly. The slides will then be submitted to the pathologist with the accompanying paperwork.

As with necropsy data, there may be a computer program or a paper *pro forma* that accompanies the tissues from each animal. Many laboratories still use paper records because computer programs do not cope well with the multiple tasks that are required over a prolonged period for histological processing of each study. Histological processing may still be required many years after the completion of the in-life phase of a study and computer programs can be difficult to re-activate after long periods.

The paperwork that accompanies tissue processing through the histology laboratory may have been generated in necropsy or may have had data from necropsy transferred on to it. A checklist of tissues processed and sectioned is required with the facility for recording the re-cutting, re-sampling, re-staining and re-embedding of tissues as well as additional findings and text comments.

At each stage of histological processing, the paperwork will require entries from technical staff with countersigned check boxes. The paperwork or authorised copies should always accompany the slides.

### 23.4.7 Histopathology

Some of the most important data that are acquired in the pathological evaluation are subjective opinions generated by the pathologist, which are not accessible to most of the routine procedures of QA inspectors.

Sections from regulatory studies must be examined by a suitably trained pathologist. Regulations are generally quite vague with regard to the qualifications and experience required to carry out such an examination, but it is implicit in the appointment of the pathologist by management that they consider them capable of carrying out the task competently.

### 23.4.8 The Pathologist

The key figure in the generation of histopathology data is the study pathologist. Within the industry, it is recognised that toxicological pathologists can come from a variety of academic backgrounds and that their working experience is quite variable. Toxicological pathology is a distinct specialty that requires modification of the techniques and skills used in the diagnostic pathology practised in university departments, and relevant experience in the field is the most important adjunct to basic academic training.

**23.4.8.1 Training and Qualifications.** The majority of toxicological pathologists hold a veterinary qualification and some also have post-graduate qualifications in pathology or a related discipline. The qualifications vary with country and include Membership of the Royal College of Pathologists, Diploma of the American College of Veterinary Pathology or Diploma of the European College of Veterinary Pathology. None of these qualifications has greater proven benefit than the others. A veterinary degree, however, is not essential and graduates from other disciplines (medicine, dentistry, biological sciences, pharmacology) bring essential diversity and varied skills to toxicological pathology.

There is no 'ideal' academic background for a toxicological pathologist, although there is increasing pressure by many employers to hire veterinary graduates. Irrespective of their background, many histopathologists are required to spend many hours a day at the microscope and some find this work pattern untenable. The experience and the ability to perform the job are important considerations when assessing the ability of toxicological pathologists rather than mere paper qualifications.

It must be borne in mind that academic background, relevant post-graduate qualifications and suitable experience all combine to make a competent pathologist. There are some initiatives to summarise the qualifications and experience of pathologists by a process of central registration. While this may serve a useful purpose in collating the credentials of each pathologist, it must be recognised that this procedure falls short of providing any kind of warranty on the studies conducted by that individual.

Documentary evidence of training and experience alone is rarely sufficient to be a reasonable warranty of a pathological evaluation and the only way to be reasonably sure of the veracity of the report is to conduct a peer review.

### 23.4.9 Histology

Histological sections prepared from animals on test are examined microscopically by the study pathologist(s) and his/her diagnoses are recorded. The appearance of the tissue is assessed visually at a range of magnifications from 10 $\times$  (or less) to 4000 $\times$  or more. The tissue sections are stained in various shades of pink and blue (with haematoxylin and eosin), and the pathologist is required to identify any differences from the expected normal appearance.

There is a basic structure for each tissue that forms recognisable patterns that the pathologist will remember and compare with other animals as well as using their memory of the expected configuration. The expected pattern will vary from tissue to tissue, species to species and with age. This means that the exercise of diagnosis involves perceptual ability, visual acuity and pattern recognition, with short- (direct comparison) and long-term (learning and education) memory skills. In addition, the patterns and appearances may become more familiar with prolonged experience and the growing understanding of pathological processes will help to place new or unusual appearances into context. With experience, operating speed and accuracy will usually increase.

Many pathological processes represent a continuum from a normal appearance to a severe disease state. The identification of subtle changes and their grade allocation, therefore, is a highly skilled job and it is no surprise to pathologists that automated, machine-based processes are limited in their capacity to replace the human eye. Indeed, comparisons between machine-based analysis and humans clearly demonstrate the superiority of the latter.

To many non-pathologists, the biggest surprise is how reliable a pathological diagnosis proves to be. This is mainly due to the extensive and continued training of pathologists reinforced by constant review and personal professionalism. This does not mean that mistakes are not to be expected and only those methods for the detection of potential errors must be incorporated into operational procedures.

### 23.4.10 Equipment

The pathologist must have access to a suitable and adequately maintained microscope with sufficient objectives to perform a thorough and efficient examination of the tissues. Obviously, the working environment should be suitable for sustained periods of concentrated microscopy.

Results of the examination must be recorded on a hand-written *pro forma* by tape recorder or direct entry into a computer program. The equipment and programs must be suitable for the task at hand and computers must operate at a suitable speed.

### 23.4.11 Raw Data

The raw histopathology data is often defined as the histological sections and blocks (by some) along with the study pathologist's final, signed opinion (by most). The histological slides can remain readable for very long periods if prepared and stored properly and further sections can be cut from wax blocks even decades after preparation and fixed tissues can be processed after 100 years or more. Some sections are not readable and blocks cannot always be re-cut to provide valid data. Regulatory decisions however are based on the pathologist's opinions and not the blocks or slides.

Written or computer records that are not finalised (*i.e.* signed off) are regarded as interim notes and should *not* become part of the audit trail. Some computer programs however impose an audit trail from the outset and the pathologist has no option to change his mind without generating an audit trail. Most pathologists do not feel comfortable committing their preliminary thoughts to a system that documents that process, as they may change their diagnosis several times. If they are not comfortable, they may devise ways of concealing their thought processes from an auditor at the risk of compromising the final result (*e.g.* *ad hoc* hand-written notes that may become lost, unintelligible or destroyed).

### 23.4.12 Number of Pathologists Per Study

Regulatory agencies permit more than one pathologist to be involved in the examination of tissues from a study. This is not widely regarded as an optimal procedure and most would not recommend more than two for any study. Indeed, one pathologist is optimal. If two or more are used, then the allocation of animals or tissues must be carefully considered (*e.g.* one sex each) and there must be regular and frequent cross reference throughout the evaluation.

Peer review procedures may need to be more stringent where more than one pathologist is used for a study.

## 23.5 MACROSCOPIC–MICROSCOPIC CORRELATION

Any finding made at necropsy or histological processing must be addressed in the histopathology examination. This should comprise a positive statement that a particular microscopic change is responsible for the macroscopic comment or that no correlation could be made or is appropriate.

Some computer programs allow this link to be made as one of their functions. Hand-written forms will need a written comment. The practice of assuming that *any* histological finding accounts for the macroscopic findings in that same tissue without a positive comment should be discouraged.

### 23.5.1 Check of Required Tissues

There should be a means of verifying that all tissues required by the Study Plan and submitted by the histology laboratory have been examined. This usually comprises a positive entry against each tissue examined in a *pro forma* or on the computer program. These entries should be made tissue by tissue rather than with a 'global' assignation of examination of tissues from an animal or study.

### 23.5.2 Nomenclature and Diagnostic Criteria

It is advisable that the nomenclature and diagnostic criteria used in studies are widely accepted and supported by published works. The diagnostic criteria and nomenclature for lesions in oncogenicity studies are readily available (STP SSNDC, RITA) and are widely used although they should only form the *basis* for diagnoses. Variations and anomalies occur and the pathologist must react accordingly. For non-neoplastic lesions, there are fewer consensuses and a wider range of terms is used.

If specific criteria and nomenclature are used, any guideline should be readily available to the pathologist. Significant deviations from the guidelines should be documented in the report.

### 23.5.3 Computer Systems

Computer programs are widely used in the generation of histopathology reports, but it should not be assumed that they are used for all studies from all laboratories.

Any computer program used must be suitable for the task and have been validated by the vendor as to their reliability and accuracy. In addition, the user must perform an acceptability testing procedure to ensure that the system operates as specified and performs the functions required (Chapter 37).

A number of commercially available programs have been used over the years along with some custom-designed software commissioned by individual laboratories. All must comply with the regulatory guidelines for computer programs as defined by the agencies to which they submit their work.

A number of issues are highlighted by the guidelines and must be incorporated into the design and testing of programs:

- Security
- Reliability
- Accuracy
- Back up
- Exportable data
- Documented validation.

In such a short chapter as this, it is impossible to deal with each item in detail and only broad topics can be briefly described.

**23.5.3.1 Security.** The integrity of the data generated by a pathologist must be protected from accidental or deliberate corruption. This usually involves several layers of password protection of computer systems and retrieval of data after hardware or software crashes.

**23.5.3.2 Reliability.** The data entered must be stored accurately without loss or corruption and must be sufficiently clear to the pathologist as it is entered to prevent the entry of inappropriate information by accident (*e.g.* entering data for the wrong tissue or animal).

The program must clearly display the animal identification and incorporate checks for completeness of the data that may be required for its internal management systems. Statistical analyses must be accurate and any algorithms used should be tested and validated by the vendor.

**23.5.3.3 Accuracy.** Systems used for the acquisition of machine-generated data must be tested for accuracy. For histopathology data, data acquisition, deletion and amendment must be tested. Reporting systems must accurately represent the findings required by the pathologist without loss or corruption.

**23.5.3.4 Exported Data.** Some regulatory agencies (*e.g.* FDA) require the provision of tumour data as electronic files (currently SAS export files) so that they can perform their own statistical analysis.

**23.5.3.5 Back up.** Data must be saved to storage media at regular intervals so that information is not lost by hardware defects or power interruption. The interval between back ups may vary between laboratories but it is inadvisable to allow the loss of substantial amounts of work (*e.g.* each

working session or not less than daily). The back up may be on a system-wide basis or just for each study.

Following completion of a study, it should be possible to restore data to a functional state on a computer system if required, although data entry may be disabled.

**23.5.3.6 Validation.** The vendor and user tests must be documented and stored appropriately. Access to the program code is usually required but need only to be held by one party.

Each new version of software should be tested by both vendor and user and documented accordingly. The testing strategy should be defined for each part of the process. The current version of the software may be installed for users once approved.

## **23.5.4 Results and Reporting**

When the evaluation of tissues is complete, the results are tabulated and a narrative report is prepared. The pathology data that can be accumulated may be massive in a 720-rat-oncogenicity study with 55 or more tissue sections to examine in each. With a large number of spontaneous lesions in aged animals, there are likely to be more than 30,000 diagnoses. These results need to be represented in both a tabular form and as detailed, complete data for each individual animal.

There is no standard method for reporting and there is a wide range of report formats between laboratories, although in all cases the findings of the evaluation should be tabulated along with a narrative by the pathologist. It may be left to the study pathologist to choose the format of the report or it may be prescribed by company policy or specific regulatory requirements.

The presentation of findings must be scientifically valid and should not obscure any important findings. This means that decisions must be taken about the separation (or combination) of results from decedents and terminal sacrifice animals and the combination of relevant data from different tissues.

**23.5.4.1 Statistical Analysis.** Tumour data from carcinogenicity studies is usually subjected to statistical analysis (Chapter 32). The methods used must be validated and appropriate, which may require the intervention of a professional statistician.

## **23.5.5 Workload**

Most studies must be evaluated within very tight deadlines and there is considerable time pressure on the study pathologist. Each individual has different capacities but excessive workloads lead to errors and potential health problems for the pathologist. The workload for each individual must be managed appropriately.

## **23.6 QUALITY CONTROL AND QUALITY ASSURANCE**

The checking of the completeness, accuracy and interpretation of data generated by the study pathologist is an essential feature of pathology quality control (QC).

The review of diagnoses and reporting by a member of the pathology department is often a routine function in pathology departments. It does not, however, comprise a QA exercise when conducted by peers within the same management structure.

Peer review, when conducted independent of the originating department, by an experienced pathologist, can constitute a QA exercise of the procedures adopted and the scientific data generated. Independent peer review, therefore, can carry considerable weight with regulatory agencies.



### 23.6.1 Personal Quality Control; Diagnostic Drift

Toxicological pathology involves making numerous (sometimes subtle and difficult) diagnoses in large groups of animals and it can be difficult to ensure that there is a consistent application of diagnostic criteria from beginning to end without drift or bias creeping in.

Diagnostic drift is the gradual divergence of diagnosis or grading of lesions from the pathologist's own standard during the course of the evaluation. It is recognised by most pathologists as virtually inevitable as the number of animals or critical diagnoses increases in a study.

Before the study pathologist submits the results of an evaluation for external scrutiny, it is necessary for him/her to be sure that the results will withstand close examination from their peers and that the interpretation is supported by other results from the study as well as being scientifically valid.

This may involve a re-examination of some tissues in order to refine some diagnoses and grade levels as well as to check for oversights, drifts and omissions. Unless the pathologist is extremely confident of their abilities, they should perform some kind of personal review even before submitting findings to the supervisor, departmental head or study director. The review may involve an *ad hoc* blind re-evaluation of some tissues or a simple re-examination of contentious or difficult slides.

A lack of a personal QC strategy is a common potential source of error.

### 23.6.2 Peer Review

It should be emphasised that peer review is ideally conducted on a *draft* report and not a final, issued report. The data in a draft is not considered to be raw data and can be changed in response to the review with relative impunity.

A review conducted on a final report will require an amendment or addendum to the final report at the very least. In some cases, a new report may be required if the study has been in circulation for a considerable period.

### 23.6.3 Departmental Quality Control

Within each department, it is reasonable to expect that there is some means of ensuring the quality of the evaluations and consistency in the work that is done and the reports that are issued. This should include a check of data integrity (*e.g.* missing tissues, macroscopic–microscopic correlation and correlation with clinical findings, clinical chemistry and haematology) as well as verification of diagnoses, standardisation of diagnostic terms and criteria and confirmation of the conclusions drawn.

The usual procedure for checking diagnoses is for each pathologist to have his work scrutinised by another member of the department. The checking pathologist may or may not be senior to the originator of the work, but it helps if he is. This procedure is often called 'internal peer review' but is really a QC procedure rather than a QA procedure.

As ever, the outcome will be influenced by the nature of the procedure and it should be realised that any review has its limitations. The greater the sample size the more reliable the process, but there must be a compromise between time, cost and thoroughness of the review.

The integrity of some of the data (*e.g.* macro–micro correlation, completeness of the evaluation) can be checked by clerical staff, but resources are rarely allocated for this task and the pathologist is expected to undertake these checks himself.

Often the data review is followed by a review of the report by another senior pathologist or the head of department before release to the study director. This is a sensible procedure that can also trap errors of interpretation.



### 23.6.4 Independent Review of the Pathology Findings

It is often claimed that the internal review procedure is as good as an external review and that may be true in many instances but it is not always the case.

Internal review can be influenced by the psychological dynamics of the group, commercial considerations, pressure of work and personal relationships. Feelings of friendship, loyalty, jealousy, enmity, inferiority, awe, deference or intimidation can all affect the objectivity of a review.

In a small well-established group, it may be seen as inappropriate to check for missed diagnoses in a random sample of tissues and only target tissues identified by the study pathologist are reviewed in some departments. In addition, over a period of years of working together, pathologists may become so closely attuned that they think similarly and may begin to deviate from commonly accepted standards as a group. In this instance, some errors will not be recognisable to the whole group.

In addition, junior members of a department reviewing their seniors may feel uncomfortable pointing out potential errors and can be persuaded to change their opinion (sometimes erroneously) by the more senior member of staff.

When the review is undertaken by a pathologist of suitable experience from outside the management structure of the department, however, it is possible to regard the review as a QA exercise. As the reviewer is not a part of the management structure that originated the findings and has a professional reputation of independence and fairness to maintain, it should be easier for him/her to remain impartial and objective about the findings. The person employed may be an independent consultant or from a different company or a CRO.

It is usual for pathologists conducting independent peer review to have a wide range of experience and most are practitioners of many years standing.

**23.6.4.1 Histology Check.** In some instances it is advisable or necessary to check the histological processing in detail. This will require an examination of paperwork along with the relevant wet tissue, wax blocks and slides. An experienced histology technician may be required to conduct the assessment, especially for the correspondence of tissues on slides with the relevant wax blocks. If some of the slides do not correspond to their wax blocks or paperwork a serious error may occur, which would require further, thorough investigation.

**23.6.4.2 Report Review.** The first phase of a peer review is likely to be the critical examination of the study pathologist's report. This document will outline the pathologist's findings and may highlight any potential issues for the reviewer. In addition, an experienced reviewing pathologist will also be able to detect potential problems from unexpected incidences, odd terminology and omission of data that might reasonably be expected to be present.

Using the tables provided, it will be necessary to check tissue accountability, macro–micro correlation as well as cause of death, data completeness and narrative interpretation of the findings. It is not unusual for effects of treatment to be attributed wrongly or for significant incidences to be overlooked in the report even though all the diagnoses may be correct.

As a result of the report review, the extent and nature of the review may need to be changed.

**23.6.4.3 Slide Review.** The design of a review should be flexible with regard to the random sample of animals to be re-examined in full. The size of the sample usually varies with the type of study and a greater proportion of animals may be examined in a sub-acute study in primates than in a 6-month study in rodents. In large studies, 10% of top-dose and control animals are often selected, but smaller studies may involve a greater proportion of the animals. It may be advantageous to include more treated animals than controls in short-term studies. It should be realised that a relatively subtle lesion occurring in 25% of animals may not be detected reliably in a 10% check of animals.

In addition to the random sample, target organs defined by the study pathologist as well as any detected in the 10% check are likely to be examined. In carcinogenicity studies, a proportion of tumours (and focal hyperplastic lesions in some cases) are also likely to be checked (from 10% to 100%).

The latest CPMP guidelines now *require* peer review for a carcinogenicity study, with at least 10% of *all animals* reviewed in full and 10% or more of all previously diagnosed tumours as well as all target organs. This is a departure for a regulatory agency and the methodology can be criticised for its lack of efficiency, as re-examination of 10% of *all animals* is not likely to serve a useful purpose in a study where no effects of treatment are seen at the highest dosage level.

**23.6.4.4 Recording Peer Review Findings.** There are various means of recording peer review data from written notes scribbled on the study pathologist's individual animal data sheets (IADSs) to customised software that documents all aspects of the process. There is no single, ideal method for all circumstances.

The findings of the review from an uncompleted study (prospective review) are not usually considered to constitute raw data, but are only regarded as interim notes that may be destroyed following completion of the review. Some companies will keep the notes on file but will not formally report them while others may prepare a full peer review report that is included as an appendix to the study report or just kept on file.

Whatever the method, the documentation of the process requires that the original pathologist's findings be presented so that the reviewer can advise that he/she modifies, adds or removes one or more findings. The original pathologist must then be allowed to re-examine the slides and accept, modify or reject the recommendations of the reviewing pathologist.

**23.6.4.5 Computer Programs.** There are relatively few computer programs that are designed for peer review of data from a range of data-capture programs. Some data-capture software also has a module for internal peer review of studies but cannot cope with data from other systems.

For external review, the software must be capable of importing data from a variety of other data-capture systems. This will allow the review of findings from a variety of different facilities that may use different data-capture systems.

A commercial spreadsheet program allows pathology review findings to be presented alongside the original pathologist's as long as the original findings can be imported efficiently or transcribed accurately from the original report.

**23.6.4.6 Hand-Written Records.** These are more common than the use of computer programs. In general, the reviewer's comments are hand-written on the original pathologist's IADSs. There are inherent disadvantages that can be imposed by the format of the IADS making the review more difficult if they do not have sufficient room for adding peer review comments.

**23.6.4.7 Resolution.** Any differences of opinion between the study pathologist and reviewer must be resolved to everyone's satisfaction – sometimes following discussion round a double-headed microscope. The means of resolution of differences of opinion and achieving a consensus must be agreed upon in advance.

There are usually three possible resolutions:

- The study pathologist agrees with the reviewer's finding and amends the database accordingly
- The study pathologist disagrees with the reviewer's findings and it is agreed that no change is made to the database

- The study pathologist agrees that there is a relevant lesion that has not been addressed but proposes a third diagnosis that is acceptable to the reviewer.

The fourth option is that agreement cannot be reached about an important lesion (*i.e.* one that has a significant bearing on the interpretation of the findings with regard to the effects of treatment). In this case, there must be a strategy in place to resolve the issue.

This exigency is very rare and it is important to ensure that the impasse is based on scientific principles and is not attributable to intransigence by either party. The resolution of the impasse may be a second review by another independent pathologist or the formation of a pathology working group (PWG).

**23.6.4.8 Reporting.** After the findings of the review have been discussed, amendments may be made to the study pathologist's data, tables and narrative reports. These must be checked by the reviewing pathologist or a clerical assistant to ensure that all of the agreed changes have been made and that the new results have been assessed and reported appropriately.

With hand-written recording procedures, this part of the review process may not be documented optimally. In small studies, this may not be regarded as a shortcoming, but in oncogenicity studies there is greater scope for errors or oversight.

Some companies prepare a formal report of the review with detailed appendices of the review findings and the actions taken. This report may be appended to the study report or merely kept on file. Others destroy all records and only keep a certificate detailing the procedure undertaken and the agreement of the reviewing pathologist and study pathologist over the diagnoses reviewed.

**23.6.4.9 Storage of Records.** There are no agreed standards for the storage of records made during a prospective peer review, although the CPMP guidelines require them to be kept. A retrospective peer review should be fully documented.

**23.6.4.10 Certification.** It is usual for a peer review certificate or statement to be produced outlining the extent of the review and that all outstanding issues were resolved. The study pathologist and reviewing pathologist are usually required to sign the document, which is then included in the study report.

## **23.6.5 Second Opinion**

An unsatisfactory set of pathology results may lead to a request from senior management for a second opinion rather than a peer review. Dissatisfaction may arise before or after the release of the original report and may come after many years of use of the test compound. This request may mark the start of a prolonged process of review and re-evaluation to confirm or refute the original findings. If the original report is not finalised, any second opinion should probably be replaced by an independent peer review.

It must be remembered that while there is only one authorised study report (containing the opinion of the study pathologist), the slides can be examined innumerable times by an indeterminate number of pathologists with the production of a similar number of opinions. The means of handling any new set of results (other than a peer review) is not generally agreed upon, but an internal report or unofficial opinion – while useful to management – is unlikely to be acceptable in a regulatory submission.

The original (finalised) report should only be modified by another official report, which may necessitate the production of a new (separate) Study Plan for histopathological re-evaluation. This second official set of data could subsequently be resolved by comparison and discussion between the two pathologists, although this is not always feasible.

### 23.6.6 Pathology Working Group

The PWGs are a panel of pathologists where each individual makes an independent evaluation of slides as part of a group exercise. The group comprises a chairperson and an uneven number of panel members.

The PWG may serve a number of functions:

- To resolve important differences between a study pathologist and a peer reviewer
- As a regulatory requirement (EPA)
- To provide an expert opinion on contentious findings.

There are several important elements of the *modus operandi* of a PWG:

- PWG members are selected carefully for their ability and expertise
- There is an odd number of PWG panel members
- PWG panel members are adequately briefed about the nature of the problem before they start
- PWG members agree upon the diagnostic criteria they are to use in advance of the evaluation
- Slides for review are selected in advance by the chairperson or other experienced pathologists
- Slides are evaluated without knowledge of the treatment (*i.e.* blind)
- Each pathologist records their diagnosis for each slide on a *pro forma*
- PWG members can re-examine some slides and change their diagnosis before the results are decoded
- PWG diagnosis will be decided by a simple majority decision
- The chairperson, at his/her discretion, may ask the panel to reconsider some cases before accepting the final diagnosis
- No more than about 100 slides/day are submitted to the panel to avoid fatigue and inconsistency.

The PWG will be constituted differently according to its function.

To resolve the issues between a reviewer and a study pathologist, the two main protagonists should be included in the PWG along with at least three pathologists who have extensive experience of the issue that has arisen.

For an expert opinion, it may be necessary to have only three members of a PWG if insufficient suitable experts can be recruited.

The role of the chairperson is critical as he/she has control over the decision-making process and is also responsible for recording the results of the PWG and compiling the report. In addition, she/he must ensure fairness in the evaluation and smooth operation of the group to make the process efficient and cost effective.

As with all review procedures, PWGs are not infallible. The quality of the final opinion is determined by the ability and experience of the panel as well as the time allocated to the task and the number (and quality) of slides examined. Additional factors that can influence the outcome are the dynamics of the group (*e.g.* a dominant or intransigent personality in the group) and the conservative or liberal approach of each member to the problem presented.

### FURTHER READING

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## CHAPTER 24

# Good Laboratory Practice in Ecotoxicology and Field Studies

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### 24.1 INTRODUCTION

It will be clear from previous chapters that legislation to control the manufacture, marketing and use of chemical and biological materials is now in place worldwide. The laws are intended to protect both humans and the environment. Manufacturers or importers of chemicals are generally required to submit considerable amounts of data on their products or potential products to government regulatory authorities so that hazards and safe use can be assessed rationally and the appropriate control measures enacted. The quality and reliability of the scientific data submitted to the regulators are crucial to these processes. The regulatory authorities in most parts of the world have therefore been demanding increasingly that all such scientific data are produced in compliance with Good Laboratory Practice (GLP) principles.

Ecotoxicology refers to the scientific study of the effects of potentially toxic substances on complete ecosystems or on single species in their natural environments. Although some of the tests, required to assess environmental safety, are best performed on a small scale in the controlled conditions of conventional indoor laboratories, many other tests are meaningful only when key phases of the work are conducted in the open air, which is sometimes referred to as the “field laboratory”. Further field studies are necessary in order to determine the behaviour and ultimate fate of substances after their release into the environment. A large element of fieldwork is also essential in some of the tests that focus on health effects in humans rather than on the environment; for example crop residue studies. The experimental work is of such a nature that, from the point of view of compliance with GLP principles, all of these field studies are more appropriately considered along with ecotoxicology rather than with other aspects of health effects testing carried out in indoor laboratories.

### 24.2 GLP REGULATIONS FOR ECOTOX AND FIELD STUDIES

In 1983 the US Environmental Protection Agency (EPA), under the Toxic Substances Control Act (TOSCA) that regulates industrial chemicals, introduced a GLP final rule applicable to ecological effects testing that included some studies in the field. At the same time a similar GLP final rule was applied by the EPA to health effects testing under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) legislation for pesticides. When both GLP rules were revised in 1989, the FIFRA GLP rule was extended to include the tests on the environmental effects of pesticides. GLP is also applied to the generation and handling of data required by later US laws such as the 1996 Food Quality Protection Act (FQPA).



On the global scene the OECD Council approved the OECD principles of GLP in 1981 as part of a decision on mutual acceptance of data by member countries. The Expert Group recommended that GLP should be applied to all regulatory safety testing, irrespective of the nature of the test or the proposed use of the substance tested.

In recent years it has become increasingly common for the different parts of many health and environmental safety studies to be conducted at more than one site. This was always likely to cause certain organizational difficulties if the study director was required to be present during critical phases of the work. Field studies are almost never carried out at a single site. The objectives frequently require the work to be performed not only at multiple test sites but also often at locations far away from the main laboratory facilities. In some cases the sites are separated by national boundaries and very often the key study procedures need to overlap in time. The introduction of the role of principal investigator (PI), who can act on behalf of the study director for a delegated phase and is responsible for ensuring compliance with GLP for that phase, was a great advance in the sensible application of GLP principles to regulated fieldwork. The role of PI in field studies was first described in the original version of OECD monograph No. 6 "The Application of the GLP Principles to Field Studies" (1992). The revised version of the GLP principles, adopted by the OECD Council in 1997, extended the concept further by allowing the appointment of PIs for any type of multi-site study.

For multi-site studies the current OECD GLP principles also make a clear and very helpful distinction between the test facility, which is a main laboratory conducting regulatory studies, and test sites that are the locations (perhaps a field with no buildings at all, or possibly another laboratory) at which a phase of a study is performed. This approach has been clarified still further in the most recent OECD Monograph, No. 13 (2002), "The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies". The latter also introduces for the first time in an official consensus document the terms "Lead Quality Assurance" to describe the quality assurance unit (QAU) which has been designated by the test facility management to take overall responsibility for a given study and "Test Site Quality Assurance" to describe the QAU which has been designated as responsible only for the phase of a study performed at their site (or field location).<sup>1</sup>

The OECD monograph series on Principles of GLP and Compliance Monitoring includes two other consensus documents, which have particular relevance to the conduct and Quality Assurance (QA) of field studies and ecotoxicology. These are the aforementioned OECD monograph No. 6 "The Application of the GLP Principles to Field Studies (1999)" and No. 7 "The Application of the GLP Principles to Short-term Studies" (revised 1999).<sup>2,3</sup>

The OECD GLP code was later adopted in full by the European Community.<sup>4,5</sup> Member states are thereby required to enact laws ensuring that laboratories carrying out tests on chemical substances comply with the OECD principles of GLP. Responding to these EC directives, governments across Europe introduced national GLP laws and regulations applicable to all safety testing for health and environmental effects of industrial chemicals, crop protection substances, cosmetics, food and feed additives, veterinary medicines and pharmaceutical products.

Compliance with GLP is assessed by government inspections of testing facilities, processes and studies. While GLP monitoring authorities in many countries have been performing indoor laboratory inspections and study audits for more than 20 years, the official inspection of work at field test facilities has been implemented rather more slowly. A survey published in Quasar<sup>6,7</sup> showed that only in the USA were any field inspections performed by the government inspectors before 1990. In Europe the governments of Belgium, France and the United Kingdom began inspections in 1993 and this was followed up quickly by the other members and prospective members of the EU. Elsewhere in the world field facilities in Argentina, Australia, Brazil, Canada, Mexico, New Zealand and South Africa are also now subject to some routine inspections. It is not clear from the survey how much of the inspection time is spent at the main field test facility and what proportion is spent at the field test sites located elsewhere.



In the United Kingdom, pesticides are controlled through use of the Food and Environmental Protection Act 1985, the Control of Pesticides Regulations 1986 and Plant Protection Products Regulations 1995. The UK Regulatory Authority requires the conduct of environmental and health effects testing of pesticides to conform entirely to GLP. The UK GLP Monitoring Authority, in a list of the areas of expertise that may appear on their official test laboratory GLP compliance statements, includes among others Ecosystems, Environmental Fate and Field trials.

It should be noted that current European Directives do not require efficacy trials on plant protection products to be performed in compliance with GLP. Directive 93/71/EEC(Ref. 8) requires such trials to be carried out to a standard known as good efficacy practice (GEP) in which the field trials organizations need to receive “Official Recognition”, from their national government regulators and are then expected to audit themselves rather than having a separate QAU.

### 24.3 SCOPE OF TESTS

The kind of information about a chemical or biological product that regulatory authorities demand depends on the intended purpose and on the scale of its manufacture and use. At the time of writing the regulatory authorities are still in discussion with the GLP authorities on producing definitive lists of the studies required to comply with GLP. In general, however, studies relevant to the theme of this chapter would include the following:

Toxicity tests in representative species of ecological interest. These tests would form a progression of study scale as development of the chemical proceeded, from acute or sub-acute tests in the laboratory, through small open-air studies that use little plots or enclosures in fields, orchards or ponds, and then to large-area fields or woodlands and mesocosms (artificial lakes). For a pesticide or other crop protection substance the small plot and field studies would aim to simulate commercial applications. For non-pesticide industrial chemicals similar small-scale studies would be conducted but there would be no trial based on deliberate large-scale dispersal. In all of these product categories both the aquatic and the terrestrial effects would be studied. Thus the range of test systems would cover fish, macro-invertebrates (earthworms, daphnia), phytoplankton and zooplankton, “beneficial” insects (pollinators and natural predators of pests), as well as small mammals and birds. In a large field study interest could extend over several components of the ecosystem and the interactions between them and would possibly last for several years.

Other tests are conducted to study the environmental behaviour and fate of a product, including its metabolism in plants, its degradation and mobility in soils, the effects of temperature and sunlight and any tendency it shows to accumulate in living species that might themselves be part of a food chain.

The laboratory determination of physico-chemical properties is another category of study that is relevant to environmental safety; examples include vapour pressures, hydrolytic and photolytic stability, solubility and partition coefficients. Such indoor laboratory studies fall outside the scope of this chapter but the results may be used to evaluate the significance, in risk terms, of the results of ecotoxicity and field tests or to predict the need for other specific studies. Therefore, although they are simple in scope and straightforward in organization, it is necessary for these studies too to be totally reliable and thus to be performed in compliance with GLP principles.

Studies are also needed to determine the amount of the chemical (usually in these cases a crop protection substance) or its metabolites that remain in a harvested crop or a processed food commodity following application to the crop. Further field or small plot tests are also performed to assess the magnitude of any residue that may be picked up by following crops – the so-called rotational crop studies.

With regard to fieldwork to assess human health effects perhaps the most complex studies are those which test for “operator exposure”. They are designed to assess the actual level of exposure to pesticides experienced by, for example, the operator of a big commercial spray rig during the working



**Figure 1** *Preparation of test item for application by a tractor mounted sprayer*

day (Figure 1). Each operator may be observed for a whole day, while working across large areas of open field, so that every action and opportunity for contamination can be recorded. Many samples may need to be taken (depending on the known properties and toxicology of the active ingredient) from the blood, urine, inhaled air, skin swabs and various items of protective clothing and undergarments of several operators. A large team of scientists and medical staff is usually needed to collect, label, document, preserve promptly and subsequently analyse this diverse range of specimens.

## **24.4 APPLICATION OF GLP IN FIELD CONDITIONS**

### **24.4.1 The Field Laboratory**

The scope of GLP in the field thus extends over a wide range of experimental conditions and test systems. Away from the controlled environment of the laboratory, variable factors such as the weather can interfere significantly with the execution of a study plan. Under adverse conditions staff and equipment alike come under additional stress, and this may be in situations where support is likely to be less comprehensive and less readily available than in the laboratory. When GLP is applied to work such as environmental testing in the field, the GLP principles must be pragmatically interpreted if they are to remain relevant. Some aspects peculiar to the extension of GLP into ecotoxicology and fieldwork are considered below. Study planning, organization and conduct of the work by the field scientists are discussed in the context of the role and responsibilities of the QA personnel. This is followed by a consideration of the scope and conduct of QA inspection and audit activities and some of the practical issues and potential difficulties that may arise and how they can be avoided.

### **24.4.2 Study Planning**

It is not part of the responsibility of QAU to plan studies or to comment on scientific features of the plan (Chapter 15). However, the Study Plan is the document from which the study scientists will work and against which both the conduct of the study and the final study report will be audited by the QAU. It is necessary therefore for the QAU to review the protocol and to comment on any aspect

that detracts from its usefulness as a working document. Does it address all the headings specified by the GLP regulations that are relevant to the type of study in question? More substantially, does it give a clear account of what is intended and what requires to be done? This becomes critical if relatively unsophisticated staff are involved in the study, or if a less familiar language is involved or if the venue of the work is remote so that supervision is less secure. Some experts prefer to use abbreviated Study Plans and keep the full details of methods and equipment in their standard operating procedures (SOPs) carried around everywhere (usually at the back of a vehicle). Others maintain that the study plan for certain types of field study should be a “stand alone” document. This is permissible under GLP and avoids carrying to the field the cumbersome SOP manual. It is for the management and study directors of each organization to decide what is best.

#### **24.4.3 Dates, Timings and Minor Changes to the Study Plan**

The GLP principles itemise the information that the study plan must contain, but fundamentally it must state the objectives and give full details of the experimental design and methods that are to be used. There will be a full description of the test system and the item (substance) to be tested. In addition there must be a time schedule and a list of the observations to be made. In the laboratory it should not be difficult to follow such a plan but in field studies forecasting is difficult, principally on account of variable effects that the weather will have on the course of the study. Thus, if a fixed day is set for actions such as spraying or the making of a set of observations then when that day arrives the action may not be possible or scientifically meaningful (Figure 2). Bad or unexpectedly unfavourable weather may have set in and so living organisms may not be at the required stage of development. Even laboratory studies that use organisms brought in from the wild may be disrupted for this cause. When several field studies, all subject to this kind of variability, are waiting to be performed the loading on available resources becomes even less predictable.

For these reasons the study plan for a field study cannot usually be as tightly written, with regard to times and exact locations, as can that for a laboratory study. Otherwise the study director and scientists risk having an unreasonably large number of amendments to describe changes in the conduct of the study as it proceeds. Noting deviations from the Study Plan or the SOP in the raw



**Figure 2** *Small commercial tractor mounted spray rig*

data is of course acceptable and indeed, under GLP, is essential. But if the deviations become the rule rather than the exception then the concept of planning becomes meaningless. It is sensible therefore to allow necessary flexibility in the study plan. Thus, in the schedule it is best to give date or time ranges stating the intervals during which operations must occur rather than specific dates. Alternatively, actions may be triggered by biological events rather than dates. With regard to observations, provision may be made for the study director to adjust the timing of sets of observations and assessments in accordance with the prevailing ecological circumstances. As the study proceeds and intentions are firmed up, there must be documented communication of the instructions to all who need to know. In addition the raw data must document comprehensively the actions that take place and the reasons for the decisions taken. The discretion allowed to the participants in the field must be within the limits of scientific validity, hence the importance of building a defined measure of flexibility into the study plan rather than allowing for unplanned flexibility as the need arises.

The flexibility of scheduling means of course that a fully detailed QA inspection schedule can often not be drawn up in advance. Rather, the QAU must draw up a list of phases that need to be inspected and then rely on close interaction between itself and the study scientists so that the necessary events can be observed as and when they occur.

In general, where certain items of information cannot be given in the study plan, the latter must state explicitly how that information is to be obtained and give instructions to record it in the raw data. This helps to ensure that all necessary items are included in the study file (and in the final report, if relevant) and also prompts the QA auditor to check for their presence.

#### **24.4.4 Master Schedules**

Management of each Test Facility and Test Site must produce lists showing all the studies and sites for which they are responsible. These will show the test locations, the study directors and PIs and the start and completion dates of the study phases. QA staff at the various sites need to ascertain that these are kept up to date.

#### **24.4.5 Delineation of Responsibilities**

A study cannot be reliably conducted unless the responsibilities for the various activities are clearly assigned and accepted. When the study is to be carried out wholly within one testing facility and under the authority of a single management, it is relatively easy to establish clear and continuous lines of accountability and responsibility through the study director; communication rarely becomes an issue. However, the field phase of many wildlife toxicity studies and the application and sample collecting phases of crop residue studies are usually performed at several locations which are often far away from the testing facility itself and may be in other countries. In such multi-site studies appropriate arrangements must still be made for the whole of the study, including the isolated phases, to be under adequate and continuous control. The study staff and any PIs must be able to communicate readily and promptly with the study director.

Shared responsibilities, as when the study is performed by two or more separate organizations, are even more difficult to manage. Local labour will often be employed and the remote phases may be wholly or partly entrusted to an organization nearer to the test site location. The study documentation must demonstrate continuity of control across any organizational interfaces. Before collaboration is agreed upon or a contract placed the sponsor should ensure that the proposed collaborator has the capability not only to perform the work technically but also to work in compliance with GLP. Are the facilities and equipment adequate? Does the organization have sufficient qualified and experienced staff? Are there viable test site QA arrangements? Do the staff know how to work in compliance with GLP? Where non-scientific staff are employed on a casual

basis, will experienced and established personnel be available to instruct and supervise the casual workers properly? The study plan must identify the test sites to be used, the organizations engaged in the study and the responsibilities of the various parties. If, owing to the remoteness of the experimental sites, day-to-day supervision cannot be given by the study director then one or more PIs must be appointed. The functions and limits of authority of the PI in accordance with GLP principles should be stated either in the relevant SOP of the testing facility or in the study plan. The study plan must state the names and addresses of the PIs and the phases of the study delegated to them. The study plan is often a convenient place to state also the contact details of the lead QA and test site QA units.

When parts of a study are to be performed by separate organizations it is best to partition the work as simply as possible. Where possible each phase is executed and reported by one PI and his team and audited routinely by the local (test site) QA unit. In this way problems associated with the interfacing of co-operating disciplines can be minimized. In a collaborative relationship such as that outlined above the following points are important: the PI and QA unit at each location will liaise closely with the study director and also report to their own managements (to preserve accountability), the staff of each organization will work in accordance with their own organization's SOP (or else special training must be demonstrated), there will be a single line of liaison between the sponsor and the test facility management, and strict formality of communication must be observed especially in the transmission of instructions (study plan and amendments) and of results (final report). Mobile phones have revolutionized verbal and textual communication for most locations but have their limitations in some rural and mountainous areas. The casual use (and deletion) of e-mails alone to convey important study information or instructions is not acceptable for GLP; there needs always to be a permanent record of some sort in the raw data.

#### **24.4.6 Standard Operating Procedures**

As with study plans, so with SOPs. The QAU has no role in developing scientific processes and methods or in assuring their scientific validity. However, there can be no proper control of quality, nor can the QAU conduct effective audits, unless there are clear written definitions of the procedures to be performed. So the QAU usually participates in the SOP preparation process to ensure that the resulting document gives an auditable account of the procedure. The QAU may also need to advise management when a new SOP or the revision of an existing one is required in order to maintain standards. Staff working in the field no less than in the indoor laboratory need to have access to copies of all SOPs relevant to the equipment and procedures to be used. This might be achieved by carrying a set of paper SOPs, as discussed previously, or by using a suitable laptop computer carrying electronic SOPs. Whatever system is used QA will need to be checking that the relevant SOPs are available and that these are the current versions.

#### **24.4.7 Test and Reference Item Identity, Handling and Storage**

The test item and also any reference substances need to be fully identified in the study plan. Where they are formulated products, both the active ingredient and the formulation identity should be stated. In laboratory studies it is usually possible to cite a unique batch identification that enables the characterization records to be checked, but this may not always be possible in field situations. Large-scale ecotoxicology trials in foreign countries are sometimes carried out using locally synthesized or formulated material, procured locally shortly before the application. In these cases the study plan should instruct that batch identification is to be recorded in the raw data and should specify what characterization is required.

Facilities for adequate storage and handling of the test item and for the appropriate disposal of any unused materials are particularly important for field studies, more so when big trials using large



amounts of materials are being conducted. There may be a laboratory at or near to the test sites, which will have arrangements in compliance with local regulations for the safe storage of chemicals and disposal of waste. PIs for fieldwork sometimes operate from a home base with storage or office facilities, or both, in an adjacent building provided by the employer. The appropriate procedures and facilities should certainly always be put in place before the need to use them arises.

Security from theft, damage and spillage and the protection of the test materials from extremes of temperature are important considerations. If samples of the test or control articles are to be retained for analysis, the study plan should state this and should specify packaging, labelling, storage and despatch instructions, taking due account of all relevant transport and export/import control requirements.

#### **24.4.8 Specimens**

In respect of field ecotoxicity studies and of residue trials, there will be a particular need to document the procedures for handling and transmission of study specimens originating from the field situation. These may include crop or soil samples or animal carcasses sent for identification or chemical analysis. Not only should the materials be sampled in accordance with the study plan, but there is a further need to avoid cross-contamination, to minimize loss or transformation of the analyte and to preserve the authenticity of the samples between the point of collection and the point of analysis in the laboratory. The SOP must therefore address packaging, storage and transport requirements, as well as identification and documentation procedures that provide a continuous chain of custody for the sample. Specimens intended for trace-level chemical analysis, as in crop “magnitude of residue” studies, have only a limited useful life even when deep frozen so there is little point in retaining them for a longer term to enable future reconstruction of the study. Similarly for samples of insect specimens taken for taxonomic classification, since such examination is often destructive of the specimen. Therefore in many ecotoxicology studies it is generally adequate to retain the specimens only for a short time after issue of the final report.

#### **24.4.9 Reference Standards**

Analytical standards form the ultimate basis of measurement in all studies with chemicals. They are of course relevant only to the laboratory phase of most field studies, therefore, will not be considered in detail here. But a brief discussion is appropriate because the QA auditors of field study work frequently become involved in auditing the complete final report including the associated analytical work. In most cases the standards will be samples or solutions of the test substance, of carefully determined and authenticated purity, procured from a specialist laboratory. Testing laboratories must have well-defined mechanisms for the management of analytical standards, which will be documented in SOPs. Records that demonstrate the origin and usage of each standard may be kept centrally. Experimental records of serial dilution and use of the standards must enable the history of each reference solution to be traced back to its origin, where the raw data upon which the characterization of the standard is based must be available. QA must pay special attention to monitoring adherence to the approved mechanisms for managing these materials and ensuring that they are fully characterized. QA auditors will need to be able to follow the audit trail for standards and to understand and verify the analytical procedures and calculations.

#### **24.4.10 Storage and Transport Facilities for Specimens**

In the laboratory sound management of incoming specimens from field studies for analysis or assessment requires appropriate and adequate storage facilities. These may have to cope with heavy seasonal influxes of material, whereas the subsequent processing of the samples will be spread out

over the year. The conditions of storage must maintain the stability of the samples, while the accommodation should facilitate the avoidance of cross-contamination or confusion of identity between them. A very large freezer store adjacent to the laboratory is the commonest solution, sometimes supplemented during periods of peak activity by hired freezer trailers or off-site commercial freezer facilities (thus adding yet another dimension to the concept of the multi-site study and another item to be included in the QA visiting schedule!).

It is away from the laboratory, where improvisation can become the daily habit, that greater vigilance will be needed. Here the QAU can do much to aid the smooth running of a study by prompting advance consideration of the storage, transport and handling difficulties that are likely to be encountered. This is best done by having standard procedures established for study specimen logistics in general, ensuring that staff are trained in their use and then auditing them when they are activated for individual studies (Figure 3).

There is a vital need to have adequate secure accommodation at or near the field site where specimens can be labelled, sorted, registered and temporarily stored. There should be at least a minimum of protection for the test items and specimens from extremes or sudden changes of weather. Good facilities will have refrigerators and freezers and plenty of bench space. For work at remote open field sites the field scientist's vehicle provides mobile working space and shelter, while insulated cool boxes and coolants such as solid carbon dioxide may be used to preserve the specimens temporarily while being transported to the test site store or the main laboratory store. Initial processing of the samples has to be undertaken often, adjacent to the field site or at the temporary storage location, to remove adhering soil or to reduce the bulk and weight before storage or despatch to the laboratory. In all cases and at every stage the preservation of identity and the avoidance of contamination and deterioration are crucial.



**Figure 3** *Improvised desk and bench space for handling specimens*



### 24.4.11 Equipment

The equipment used in laboratory ecotoxicology studies requires the same systems of use and control as other laboratory equipment and presents no special problems for QA, but in the field situation particular difficulties may arise. When equipment is to be used at a field site, far away from the laboratory base or other immediate help, particular attention must be paid to robustness and reliability (Figure 4). It is important to check apparatus before it is deployed, and for the field team to carry appropriate manuals, spares and accessories or back-up equipment. To enable full monitoring of critical equipment by the QAU, as well as reliable use by the staff, the relevant SOP and if necessary the maintenance record should accompany each instrument in the field just as in the laboratory. Problems can arise when the equipment is not owned by the laboratory but by a collaborator, for example a farmer. In these instances, since historical calibration and maintenance records are unlikely to be available, the QAU should verify that the experimental records show clearly that the equipment has been checked and calibrated immediately before use. The cleaning of equipment, particularly pesticide-spraying equipment, is a critical maintenance procedure and should be supervised by testing facility staff.

### 24.4.12 Data Recording

The open field, with the wind, rain, dust, mud and bright sunshine, is a much more hostile environment than the indoor laboratory for the meticulous recording of raw data. Every care should be taken to make the task of the field scientists as easy as possible (Figure 5).

The use of carefully assembled field notebooks or files containing standard pages or template sheets for data recording is one solution. The user is prompted to record the required information in the most efficient way. Sample and transport documentation is likewise designed to ensure that the required identification and data are recorded. Suitable files can also be used to hold the study plan, SOPs, specimen labels and headed sheets with space for writing further information in free text. The specimen labelling system should use pre-printed labels (computer-generated or bar-coded) wherever possible, since the risk of error is much less than with large numbers of hand-written ones (Figure 6). Hand-held electronic data capture systems are now sometimes used instead



**Figure 4** *Equipment for taking deep-soil samples*



**Figure 5** *Equipment for shallow soil sampling*

of paper records, but many experts believe that for GLP compliant studies the total security of *e*-data cannot yet be guaranteed in adverse field conditions.

#### **24.4.13 Staff Training**

Two peculiarities of environmental work as compared with laboratory-based toxicology appear to be – firstly, a greater tendency to use casual staff and secondly, the use of non-scientific staff, for example tractor drivers and spray operators, during critical phases. This probably reflects the need to concentrate much fieldwork in the summer, the large geographical spread of the operations, the nature of some of the technology and the relative labour intensiveness of some activities. These participants have to be trained to an extent that is commensurate with their role in the study, and there should be documentation recording the training. The QAU staff may be asked to provide the necessary instruction in GLP principles for these staff. They should check that the experimental



**Figure 6** *Downloading electronic weather data to a portable computer*

records contain documentation of technical training and briefings given, and should confirm in particular that the raw data shows evidence of proper supervision of the temporary staff by the testing facility personnel.

## **24.5 FURTHER ASPECTS OF MONITORING BY THE QAU**

The provision of appropriate facilities and resources, and the establishment of standards and plans for their use, are necessary but are not in themselves sufficient to ensure the quality and integrity of study data. GLP requires, as indicated previously, that the operations of the testing facility and the conduct of the studies are monitored by an independent group of QA staff. This requirement applies equally to ecotoxicology and fieldwork as to indoor laboratory work. The surveillance by the QAU enables recipients of the study report to have confidence that it is indeed supported by data that have been generated in accordance with the approved standards and plans.

### **24.5.1 Quality Assurance Unit**

For multi-site studies, the test facility management should designate a “lead Quality Assurance” unit to take overall responsibility for QA of the study and should inform all of the “test site QA” units of this. The lead QAU needs to ensure adequate coverage throughout each study by close

liaison with every test site QAU. In the absence of adequate coverage at a test site the lead QAU will need to make other arrangements, perhaps by sending one of its own staff or by obtaining experienced support from a consultant or another organization. Review of the study plan and audit of the final report is primarily the responsibility of the lead QAU. The test site QAU will inspect work at their site and report the results of these inspections to the PI, the test site management, the study director, the test facility management and the lead QAU.

For practical reasons the QA auditing is selective, thus attention must be directed primarily to the more critical study operations so that the effectiveness of this limited surveillance may be maximized. It is necessary to consider what are the critical phases of an ecotoxicology or field study and what QA actions are appropriate. Table 1 provides a list illustrating the general approach.

The master schedule of most organizations performing field studies will show a large number of fairly small trials of short duration (approximately 6 months) on scattered sites, and also some

**Table 1** *Monitoring of fieldwork by the Quality Assurance Unit*

*This list illustrates the main phases and summarizes QAU surveillance for studies which include operations in both laboratory and field. Where reliance is placed on non-study-specific inspections, these must be supported by audits of the study-specific experimental records and final reports.*

<i>Phase</i>	<i>QAU actions</i>
<i>Study planning</i>	Audit Study Plan and all amendments
<i>Test substance</i>	
Characterization	Data audit
Calculations for dose preparation	Audit
Dilution for dosing/application	Inspect, confirm supervision
Sampling for confirmatory analysis	(If any) Inspect
<i>Test system</i>	
Procurement/authentication (flora, fauna, crop)	Audit records
Calibration/pre-use verification (instruments)	Audit records
History of plot/crop preparation (field study)	Audit records
Layout and characteristics of plots (test sites)	Inspect
<i>Application of test item</i>	
Operator training/briefing	Confirm/participate
Calibration/pre-use verification of equipment	Inspect, confirm supervision
Application	Inspect
Sampling of “confirmatory” doses	Inspect
<i>Observations on test system</i>	
Operator training/briefing	Confirm/participate
Pre-dosing observations	Inspect
Post-dosing observations	Inspect
<i>Sampling of test system</i>	
Operator training/briefing	Confirm/participate
Pre-dosing sampling	Inspect
Post-dosing sampling(s)	Inspect
Specimen labelling	Inspect
Specimen storage/transport	Inspect
<i>Laboratory analysis of specimens</i>	
Receipt/storage/processing	Audit records
Taxonomic classification (flora, fauna)	Inspect
Chemical analysis (dose formulation, confirm application of dose, wildlife/crop/soil/ground water for residues)	Inspect
Reference standards authentication	Audit records
Chain of custody for samples	Audit records
All data and records	Audit
Final report	Audit against data, Study Plan and SOP



larger or long-term studies (up to 5 years). The QA programme needs to accommodate both of these types of study by using a mixture of procedure- and study-based inspections, supported by facility inspections at the test facility and, where there are permanent buildings, at the test sites.

The planning of any study is a critical phase and the auditing of the written study plan is therefore most important. The QAU may usefully confirm (without discussion of scientific matters) that all of the relevant professionals, in particular the PIs, have been able to give consideration to the methods of the study and its objectives. The planned field activities may be grouped according to whether they are directed towards bringing the test item to interact with the test system, such as dosing or spraying, or whether they concern the later arrangements for capturing the effects of this interaction, such as sampling or assessment.

First, the challenge or dosing phase must be considered: the calibration of any equipment to be used, preparation of the dose form and application of the test article. Several different kinds of application equipment may be used in ecotoxicology studies. In the smaller scale aquatic tests quantitative micro-syringes could be used to introduce a continuous stream of test substance into the water to maintain the desired concentration. These instruments would call for an initial calibration, and the QAU should make a point of checking the calibration records. Alternatively, there may be provision for continuous monitoring of the test substance concentration in the test medium. Then the calibration of the test-medium generator could be of secondary importance and control of the experiment is likely to reside in the analyser, which should get appropriate QA attention. Micro-syringes may also be used to apply radio-labelled test solutions drop-by-drop to leaves or fruit during plant metabolism studies (Figure 7).

In small plots or the open field the test substance is frequently applied in the form of a spray, or possibly as granules. For small-scale applications (such as in a plant metabolism study and many crop residue studies) a hand-held, gas-operated sprayer will probably be used. Generally the objective here is to apply nominally “all” of a given volume of the test solution, sometimes radioactively labelled, to an isolated small group of plants; equipment calibration problems are minimal, because the application, within the context of the experiment, is usually self-quantifying. Commercial sprayers are used for applying the dose in many crop residue and ecotoxicity field studies. These devices can range from hand-held sprayers for small plot work to tractor-mounted or aerial sprayers for large-scale application. The QAU should check that a valid calibration record,



**Figure 7** *Pre-emergence dosing for a plant metabolism study*



**Figure 8** *Small commercial granule applicator*

relevant to the current use, is available. Calibration of equipment should be undertaken or be supervised by an appropriately experienced technician; again the QAU should check for documentary evidence (Figure 8).

Preparation of the test formulation must also be regarded as a critical phase, even when carried out indoors. For large-scale applications, dilution of the test substance concentrate to working strength will usually be done in the field. In these instances mixing the spray fluid and filling the spray tank should be carried out under direct supervision of the PI. Calculations of volumes, *etc.*, should be checked and countersigned. The QAU, if not actually present during these operations, should look for documentation of this supervision in the experimental record. When the test substance is being applied, whether by automatic dilutor in the laboratory aquatic study or by machine sprayer in the field, the relevant parameters of the delivery, for example the “settings” of the equipment, should be recorded. This is necessary both to confirm proper quality control and to ensure that the operation could be reconstructed. The QAU should check for such information in the experimental records (Figure 9).

In many instances, analytical measurements to confirm acceptability of the test concentrations (or the application rate) will have been specified in the study plan. The QAU, as well as checking that the results accord sufficiently with the desired values, will also confirm that the sampling regime has complied with that planned. Correct sampling is crucial to meaningful analysis.

The making and recording of observations and the collection of test system specimens for subsequent analysis represent another critical phase. A further point to be stressed here is the need for the records to demonstrate correct handling of the samples. The sample containers should be labelled promptly along with the point and time of collection and the identity of the sampler. Moreover at data audit or final report audit, the record should show the entire history of the sample from the point of its collection to that of its subsequent analysis in the laboratory. There should be a continuous chain of custody with all of the elapsed time accounted for and every sample accounted for (Figure 10).

Finally, QA staff need to use their time as effectively as possible when visiting distant field sites. One carefully planned inspection visit can encompass a number of study phases or procedures



**Figure 9** *Harvesting rice from a miniature paddy plot*



**Figure 10** *Collection of rice from paddy field plots*



**Table 2** *Practical QA field inspection*


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<i>Before the inspection</i>	
Be informed	Read all Study Plans carefully Study the SOPs
Be prepared	Re-read previous inspection reports List any questions or comments
Be equipped	Suitably dressed and equipped for adverse conditions (cold, heat, wet, wind, mud, dust, strong sun, <i>etc.</i> ) and long waits! Clipboards, files or folders that are secure in windy and wet conditions. Use checklists and reporting templates. A camera is sometimes useful
<i>During the inspection</i>	
Be diplomatic	Learn when to stand back and be silent and when to speak up Be prepared to take advice Do not become a problem in the field through accident or ignorance (the PI may have enough problems already!)
Be persistent	Eat, drink and talk with the locals where possible Dare to ask questions; even naïve ones After finding a problem do not assume that it is the only one Use both brain and eyes
<i>After the inspection</i>	
Be efficient	Report findings promptly Phrase your questions for a realistic response
Be effective	Follow up the findings Verify agreed corrective action

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(Table 2). A visit early in the growing season to a key location may cover the early phases of several studies. Inspections can include sprayer calibration, test system layout, final dose preparation, dose application, sampling methodology, record keeping and general adherence to SOP and study plans. A second visit later in the year can be used to confirm the integrity of test sites, collection of specimens (harvest), sample labelling, handling, storage and transport, data recording and once again the general adherence to SOP and study plans. Even with the best-laid QA plans and after travelling for many kilometres, adverse weather conditions can suddenly upset the field timetable. Thus, a sudden local rise in wind velocity or the imminent threat of rain may delay spraying for hours or even days. In these situations the astute QA auditor will always find something useful to inspect until conditions improve and thus extract maximum value from the visit.

The past few years have seen several clarifications in the concepts and terminology of the internationally agreed GLP principles (and the related guidance and consensus documents), which have been of great help both to those who conduct ecotoxicology and field studies and to the QA professionals whose task is to monitor them for GLP compliance. The key to ensuring the continuing relevance and usefulness of GLP for ecotoxicology and field studies, as the regulatory requirements become more rigorous and the technology advances still further, is to revisit the underlying principles of GLP and to maintain a pragmatic approach in their application.

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# Animal Health

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## 25.1 INTRODUCTION

Clinical development requirements of animal health products have evolved a great deal over the last few decennia due to the demand for safe products of good quality with a proven efficacy. Continuous efforts to improve quality of data generated for registration combined with efforts to harmonise requirements were made to improve acceptability of dossiers by different countries and regions worldwide.

In recent years, several food scares where contaminated animal products reached the consumer again highlighted the extreme importance of safety of the food chain and any other impact on human contact with these products. It raised public awareness that safety studies for animal health products are extremely important to public health. In addition to that, ethical concerns for the well being of target animals and any economical implications support the stringent requirements on the integrity of the data. Not surprisingly, the registration of new animal health medicinal products follow largely the same principles as those for humans products requiring demonstration of safety and efficacy to authorities prior to the approval of licenses.

The GLP<sup>1</sup> requirements for safety data to support registration of animal health medicinal products are practically identical as for human medicinal products. The main differences lie in the nature of studies required but the GLP<sup>1</sup> standard used remains the same. Fields that need be tested are ecotoxicology or environmental fate studies, toxicology including in the target animal, and residue testing for food animals where the absence of unacceptable concentrations of residues must be demonstrated.

For efficacy studies, the tremendous variation in animal species and purpose, variation in disease models, housing and rearing conditions, warranted animal health-specific Good Clinical Practice (GCP) guidelines created by the various regions. Regional GCP requirements were globally harmonised during the VICH process and in July 2001, the VICH GCP<sup>2</sup> guidelines became effective for North America, Europe and Japan with Australia and New Zealand involved as observers.

Part of the scope of the VICH process was the search for a balance between good science, data integrity and excellent quality requirements allowing sufficient profitability to assure adequate development of new AH products.

With the new VICH GCP<sup>2</sup> guidelines, responsibilities regarding the assurance of quality were introduced. For the first time for Europe, Quality Assurance (QA) responsibilities were defined and guidance was given for inclusion of an independent audit required from the sponsor. The US CVM<sup>3</sup> guideline number 58 is also expanded by the guidance of a QA audit. For US AH pharmaceuticals,

general quality systems were already largely in place, whereas for biological clinical studies these were generally not present up to now. At the time of writing this, how exactly the QA role in 6 veterinary clinical studies should be fulfilled remains to be clarified. In this chapter, a review of the references to the QA role in VICH GCP<sup>2</sup> is made and an interpretation on its initial implementation in practice from a European perspective is given. No local or national requirements were taken into account.

## 25.2 VICH-GL9-GCP: GUIDANCE ON QUALITY

As defined in the introduction of VICH-GCP<sup>2</sup>, the intention of the document includes a standard for the auditing of clinical studies evaluating veterinary products and is aimed at auditors as well as those involved in the design, conduct, monitoring, recording, auditing, analysing and reporting these.

The GCP document identifies responsibilities for the QA, QC, and independent audit requirements and indicates that audit procedures should be in line with generally well-recognised and accepted principles of QA. Guidance is given for the sponsor to provide a department of auditors with sufficient separate reporting lines to allow independent reviews of systems, sites, documents and processes.

The QA auditors in the animal health industry will adopt strategies and techniques used in ICH GCP<sup>4</sup> and other quality standards adapted to the various practical situations of veterinary clinical studies. A difference in approach will be required when dealing with poultry studies with thousands of animals on one site vs. small animal patient studies which are in design closer to human health studies.

### 25.2.1 VICH-GCP<sup>2</sup> Document on QA and Auditing

QA is defined as: 1.21. *A planned and systematic process established to ensure that a study is performed and the data are collected, documented (recorded) and reported in compliance with this guidance and the applicable regulatory requirements.*

Audit is defined as 1.3. *A systematic and independent examination of study related activities and documentation to determine whether the study being evaluated is or was properly conducted and whether the data are or were recorded, analysed, and accurately reported according to the study protocol, study related standard operating procedures (SOPs), GCP and the applicable regulatory requirements.*

2,2 of the Principles include that ‘ . . . data audited to this guidance can be expected to facilitate the review process, since the regulatory authorities can have confidence in the integrity of studies which follow such re-established written procedures’.

GCP principles put the responsibilities for the QA functions with the sponsor:

2,8 *the assurance of quality of every aspect of the study is a fundamental component of sound scientific practices. The GCP principles support the use of QA procedures for clinical studies. It is perceived that the sponsor would be the party responsible for the QA functions for these studies. All participants are encouraged to adopt and adhere to generally recognised sound QA practices.*

The sponsor’s responsibilities include:

4,2,16 *Ensure the quality and integrity of data from clinical studies by implementing quality audit procedures that are consistent with well-recognised and accepted principles of QA.*

4.3.1 specifies that even when contracting out sponsor functions to a CRO, the ultimate responsibility of the quality and integrity of the data always resides with the sponsor.

The section on study documentation includes that

8.1.2 . . . *Study documentation should be audited by the sponsor’s quality audit procedures, consistent with well-recognised and accepted principles of QA. When a quality audit is conducted, the*

*auditor should prepare a report for the sponsor which details the auditing process and which certifies that the audit has been conducted.*

Thereby being indicative that QA group SOPs are required and an *audit certification by auditor* to be attached or included in the final study report consisting of the dates of site visits, audits and when reports were provided to the sponsor. (7.3.10.4)

QA should not be confused with QC: Quality control is defined as 1.22. *The operational techniques and activities undertaken within the QA system to ensure requirements for quality of the study related activities have been fulfilled.*

This is consistent with functions described for the monitor, who's responsibilities that include ensuring both the study facilities and personnel are suitable for the job and understand their responsibilities, ensure the protocol, SOPs, GCP and regulations are being implemented and verify the data.

The Monitor is described as (5,1) *an individual appointed by the sponsor to be responsible to the sponsor for monitoring and reporting on progress of the study, verifying the data and confirming that the clinical study is conducted, recorded and reported in compliance with GCP and applicable regulations* (Glossary includes to SOPs).

The report checklist gives guidance to include in the body or as an appendix the dates of monitoring visits. A written statement to confirm compliance to the principles of GCP is required from the Monitor:

*5,2,14 Confirm compliance to the principles of GCP by providing a summary report of the contacts, visits made and activities witnessed during the conduct of the study. This summary report should be submitted to the sponsor at the end of the study. And compliance is defined as adherence to the study protocol, relevant SOPs, GCP, and the applicable regulatory requirements.*

Inspections by a regulatory authority are included as a possibility and are defined in 1.16.

### 25.3 THE QUALITY ASSURANCE ROLE

The QA strategy will be based on the quality standards set by the company's management in view of regulatory and corporate requirements. Once the quality objectives are clear, a quality system to suit can be developed and QA's role is then to provide an independent and systematic examination thereof. The QA auditor's responsibility will be to audit against the defined quality system or document. They should report on the effectiveness of the quality system to management and if it is suitable to achieve quality goals. In addition, QA's role is to assess and assure the quality of elements within the quality system, report findings, ensure clearance of corrective actions and support process improvement by giving feedback. What must absolutely be avoided is the transfer of responsibility from operating staff to the auditing group by confusing QA with QC. For example 100% verification of raw data vs. the electronic data pack by the auditor, means duplication of work and extra costs at best and no independent assessment of the task being performed will be available.

The audit should stay within the scope of the audit and to the processes required to achieve the set quality goal. For example, during a site visit for a certain study, equipment not used in the study should not be assessed. For a clinical study the assessment must be to ascertain ability to conduct the study, not to ensure the site would be eligible for a 'GCP accreditation' as in the GLP area would be the case.

In animal health clinical development, the objective is normally to collect data for the registration of investigational veterinary products and the objective of the quality system set out by the sponsor is likely to meet VICH GCP<sup>2</sup> standards.

Considered for audit should be all departments, systems, SOPs, personnel and documentation that result in the generation of the required data. For each department that takes part in the process, procedures should be available that describe how the quality system is implemented in

compliance with regulatory and corporate requirements. Once departmental procedures, templates and systems used, including a CRO if one is used, have been evaluated, study audits can focus on evidence of protocol and SOP implementation.

When all this is taken into consideration, to assure that the quality of all these procedures has been implemented appropriately, the QA auditing group will need to have a systematic and comprehensive approach. To clarify the auditing scope, process and reporting, SOPs should be in place to ensure auditing methods, personnel responsibilities are clear and cover all aspects of the clinical study activities including communication between departments. How audit results are dealt with, where reports are sent and who should ensure follow up is essential to the whole process.

The auditing group will need appropriately qualified and trained personnel to ensure that the procedures are being conducted reliably and consistently. QA auditor responsibilities under VICH GCP are consistent with those under other good practices. The Sponsor will normally define these in SOPs, and ensure that training programmes are in force. Standard procedures can clarify how this should be approached and documented. Auditing itself will follow the same principles as that of Human health studies allowing for differences in requirements, in environment and animal health husbandry and techniques.

Communication with clinical development personnel regarding priorities of projects and timing of initiation of the various audits is essential. For example, the report audit is usually the last process prior to sign off, timelines of this are always under close scrutiny. To ensure that audits can be performed timely and completely, careful planning and close relationship between clinical development monitors, project leaders and auditors is needed.

## 25.4 ROLES AND RESPONSIBILITIES

Part of the scope of GCP is to ensure that good science is conducted safely and documented with the utmost integrity so that there is no doubt on the validity of the data. There should be clarity on what happened and how things were done, when and by whom, so that a complete reconstruction of the events is possible from the study documentation and there should be evidence of compliance with the protocol and SOPs. Audits will form an independent assessment thereof. Input of the QA group upfront by means of training of study personnel, review of SOPs, systems and relevant documents to ensure that they meet requirements as well as auditing as a feedback on the entire processes of study conduct and reporting and improvement of procedures as a follow up are required for continued improvement both in quality and cost-effectiveness of the whole process.

It is important to understand that quality cannot be audited into a study and it is essential that all parties clearly understand their roles and responsibilities as clarified in SOPs.

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All	Quality assurance in a clinical study is the responsibility of all involved	
Sponsor	To ensure SOPs, qualified and trained personnel and suitable material are available. Report all results once IVP was used AE reporting Carries ultimate responsibility for the Quality of the data	Implement QA audit procedures
Investigator	To implement the protocol, SOPs, GCP and collect valid data and look after animal and human safety and secure drug control	Confirm compliance by authorship of the FS report or otherwise by statement

Monitor	<p>The communication link, assisting the sponsor and the Investigator and solving problems.</p> <p>Ensure suitability of site and personnel, communication, training of study personnel</p> <p>QC-control adherence to protocol and SOPs – data verification</p> <p>Once the study is ongoing, the Monitor will normally be responsible for the quality, and visit the study regularly and certainly at key phases to ensure that the protocol and GCP are being followed</p>	Confirm compliance in a summary report
Auditor	<p>Independent check that the various processes are being implemented, <i>i.e.</i> oversees the monitoring activities and determines if the SOPs, protocol are being followed</p> <p>Examine study activities and documentation</p> <p>Ensure clearance of findings, support process improvement and performance of the organisation</p> <p>Report audit findings to relevant management</p>	Audit report for the sponsor including audit process and certification that the audit was conducted

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## 25.5 AUDITING STRATEGY

Further to corporate and regulatory requirements, a strategy as to which processes and studies at what stage and to what department will be audited should be set up.

All elements of the quality system should be considered for audit. SOPs should be developed for determining how, when, what and where to audit and how to report results to auditee and management, both direct and trends, and how to ensure follow up and clearance of findings.

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Auditing schedule contains processes and studies to be audited including timelines

Department process related audits:

Check SOPs and personnel training records and adherence to SOPs, regulatory requirements, guidelines, corporate policies are systems fit for purpose, inspect operational compliance.

Study related audits:

Check protocol adherence, and compliance to SOPs, regulations and guidelines.

Further to ICH requirements, once the quality system is in place, it could be argued that only a representative proportion of studies should be audited, depending on the type and criticality of the data collected and experience of the study personnel involved.

Auditing Plan is established for each process or study audit and will include details of exactly what, when and by whom audits will be performed.

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### 25.5.1 Audit Schedule

What to audit and when, and QA support for Animal health clinical development is normally based on following principles:

<i>Avoid errors upfront</i>	<i>Assess compliance</i>	<i>Follow-up</i>
<p>Are all personnel, systems and procedures in place and consistent with requirements</p> <ul style="list-style-type: none"> <li>• Support training of study personnel and review of drafts prior to auditing the final draft:</li> <li>• SOP review</li> <li>• Systems validation</li> <li>• Protocol review/audit</li> <li>• Pre-study site assessments</li> <li>• CRO evaluations prior to placing a study</li> <li>• Consultancy</li> </ul>	<p>Are they being implemented as planned</p> <ul style="list-style-type: none"> <li>• Process audits</li> <li>• Vendor audits</li> <li>• Study audits               <ul style="list-style-type: none"> <li>Study protocol</li> <li>Site audits</li> <li>Final Study Report</li> </ul> </li> </ul> <p>QA not QC</p>	<p>Feedback, reporting and clearance of findings</p> <p>Provide audit certificate</p> <p>Metrics and trend analysis</p> <p>Process improvement</p>

### 25.5.2 Process Audits

These should be considered for the various departments and processes that are involved in the study conduct, such as Clinical development processes, Contracted services, Biometrics, Data management, Computer systems, Regulatory affairs, Pharmacovigilance, *etc.* and include checking of:

- Organisational chart, job descriptions, CVs and training records of all personnel
- Departmental SOPs *vs.* requirements and against operational compliance.

### 25.5.3 Study Audits

These cover the various phases of study conduct and look for evidence of protocol and SOP implementation.

*25.5.3.1 Study Audits: Pre-Study – Planning Phase.* QA study activities and audit areas are spread over the entire process, whereby input in the planning phase is the largest opportunity to make a positive impact on quality.

QA checks in the planning phase include:

- Ensure systems/procedures are suitable and followed
- Site personnel are suitable
- Personnel is qualified and adequate training was undertaken
- Paperwork meets VICH GCP<sup>2</sup> and will allow accurate data collection.

Participation of auditors at clinical development project meetings is important for getting an overview of the studies planned, understanding priorities in timing, clear objectives of each study, risk assessment, and personnel and sites selected to perform each study. Best timing of study-specific visits can also be discussed especially where multi-site studies are concerned. Depending on training and experience of selected study personnel, QA oversight can be increased to suit needs. QA training for GCP compliance of both internal and external study staff can be required and discussed. More input in the draft protocol and more frequent site audits early on in the study can be scheduled for inexperienced Monitors and provides the greatest opportunity for improvement. Care must be taken not to take over the Monitor's responsibilities and perform QC. General communication with regard to changing timelines and priorities should be discussed and updated by frequent meetings.

**25.5.3.1.1 Training of Study Personnel.** Auditors may be involved in training activities undertaken for Monitors, Investigators and other study personnel with regard to GCP or SOPs. The auditor is a specialist in both GCP and relevant SOP requirements and will usually be excellently placed to convey that knowledge to internal as well as external study personnel. To assure the independent status of the auditors however, normally the control and responsibility of the training programme lies with the clinical development department of the sponsor.

For multi-site studies, there are usually pre-study meetings to ensure uniform instructions on protocol compliance and performance of assessments; other study procedures and capturing data are given. These meetings form an excellent opportunity for training sessions on GCP and relevant SOPs. It may be of great help to project staff and monitors to be supported by audit personnel to provide this training or part of it. A separate speaker to address SOPs and GCP, will emphasise the importance and focus attention on essential administrative burdens of study conduct, and will let the monitor focus on technical requirements of the protocol.

These training meetings may also be a forum to address any practical difficulties that may arise on site, for example, availability of suitable drug storage, and help to find timely and acceptable solutions.

**25.5.3.1.2 Site CRO Assessment.** To ensure a study site is suitable for a given study and site selection is a Monitor responsibility. QA's role here may be to assess whether these responsibilities have been performed as required. A site audit could also be requested prior to placement of a study, for example, for new sites or as follow up to clear previous findings.

Pre-study site assessments will focus on the sites quality system, including checks of the organisational chart, job descriptions, personnel qualification and training records to perform relevant tasks including GCP, SOPs, systems and technical requirements. The facility's overall ability to comply with regulatory requirements, SOPs, the protocol if there is one and contractual agreements will need to be assessed. This could include compliance to site SOPs, audit-relevant equipment and its maintenance programme, systems, storage procedures and facilities for data, records, IVP and control products. Audit animal facilities and operations, sample handling and trace ability. If there is a QA unit, assessments can be made from their SOPs, records, the size of the unit and whether their experience is suitable for the requirements.

CRO evaluation and laboratory audits account for the majority of pre-placement site assessments and will focus on the organisations quality system, including personnel qualification and training records to perform relevant tasks and audit existing operations against the necessary criteria of the work to be contracted.

In case data analysis and statistical services are subcontracted, the methods of data management and verification as well as statistical analysis procedures and software used and their validation should be reviewed.

Review of draft paperwork for GCP compliance, including draft protocol, CRFs, contracts, forms to document various requirements, Owner consent forms, *etc.* can be performed in the early phases of a study.

Usually, a pre-study site audit at a site other than a laboratory or CRO is performed when a protocol is available.

#### 25.5.3.2 Study Audits: Protocol Phase – Review and Audit

**25.5.3.2.1 Study Protocol.** The importance of the protocol to the success of a study cannot be overemphasised. It should fully describe the study objective, how this will be achieved, by whom and under which conditions. The protocol is usually the fruit of hard work and discussions between various departments. A carefully considered study-design, procedures and observations with their timing, locations and personnel should be included to come to a clear and easy to read protocol for the investigator performing the study and for the regulatory authority to review and assess the protocol.

The VICH GCP document includes a detailed checklist of information that should be considered for inclusion into the protocol when a study is being planned. Normally, Sponsor SOPs will include a protocol checklist or templates to comply to and will describe the internal processes and responsibilities such as protocol authorship, review and approval.

*Draft Review.* Depending on the status of the study protocol, (*i.e.* is the study unique or have similar studies been conducted or planned), and experience of the author of the protocol, more support may be required from the QA auditor at the draft protocol stage. A review of a draft protocol can be performed to advise if any required information is missing, to check the clarity of the description of procedures including instructions on handling of records and attached data capture forms and sometimes-preliminary (spot) check on consistency.

Additional documents either referred to or attached to the protocol, like the investigator brochure and informed owner consent including information to be provided to the owner should also be considered for QA review.

*Protocol Audit.* The QA audit on the protocol is normally planned once all methods, design, sample size, statistical processes, data capture, AE reporting requirements, *etc.* have been agreed and a final draft ready for signature is available. Any changes in procedures after the audit has taken place can invalidate checks made, for example, on consistency. The exact process of protocol finalisation, audit and sign off is normally specified in the sponsor SOPs and part of the audit. Responsibilities on who should receive audit findings and how to deal with them are usually included in QA and Clinical Development SOPs.

To ascertain the independent status of the auditor and to simplify the process, auditors usually do not sign the protocol. A formal process of recording which version of the protocol was audited and by whom, the timing, and any audit findings are included in an audit report, signed by the auditor and returned to the person responsible for the completion of the protocol. To ensure follow up, actions taken in response to the audit findings are documented, signed off and returned to the QA group for review when necessary. Sometimes, a re-audit could be performed if the nature of findings warrant this or if the sponsor requests this.

The protocol should be audited against SOPs and regulatory requirements. A comprehensive checklist is available in the VICH GCP<sup>2</sup> document, which is normally adopted in addition to any requirement on format or template in the sponsor's SOPs. Apart from checking the protocol for completeness, clarity and consistency following checks should be considered:

- Ensure the objective is clear and supported by procedures, data recording requirements and data summaries or statistical assessments described.

- Ensure timings are specified and clear especially for day of animal selection, days of treatment, observations and study endpoint.
- Is clear information on dosing is available, for example how the dose is calculated, dosing tables, treatment administration instructions, *etc.*
- Are procedures clearly described and alert for any unclear or ambiguous statements. For example sample collection: timing and instructions on how they should be taken, labelled, stored (refrigeration requirements, *etc.*), transported are clearly described.
- Is it clear which procedures will be carried out at which site and who is the responsible contact at each site. Are all addresses listed.
- Are any animal welfare requirements and observations clearly described and are clear instructions available on what to do and who to contact in case of abnormalities or adverse events.
- Is there consistency between the various sections of the protocol.
- Do case recording forms cover all data required by the protocol procedures.

Where translations of the protocol and attached data capture forms are required, great care should be taken that any described procedure, assessments and data capture forms are correctly translated. Any error in this area can ruin a study. Responsibilities and procedures to deal with translations should ideally be described in the sponsors' SOPs. QA responsibility will be to check that the processes are being followed, ideally check appropriate proportions if possible and report errors and to allow for improvement of the quality process.

*Suggestions from QA to Consider in the Protocol.* QA auditors may include suggestions to the author to consider in the protocol which may help avoid Amendments or Deviations later during the study. Some examples are:

- Suggest to allow flexibility, for example, in indicating time points by giving a range rather than exact time for sampling or observations to be made if possible, to avoid deviations.
- Suggest back up personnel is available and that the procedural requirements allow these personnel to perform various tasks in the protocol.

During the protocol audit, the auditor can abstract all required information to make his/her auditing plan for the study. He/she can identify key phases and plan these into his/her schedule.

**25.5.3.3 Study Audits: In Life Phase.** The scheduling of site audits may vary depending on the nature of the study, its size, complexity and experience of the Monitor and sometimes other personnel. A multi-centre study conducted in several sites in a number of different countries will require a different approach simply because logistics of getting to the sites at key phases may be impossible in the time given. It's important to assess which site(s) on which date(s) may be most informative and productive as a feedback to help improve quality. This could be key phases, experience of personnel involved, or areas where lots of errors occur, for example feed mills for the mixing of medicated feed or the collection of samples, sample handling at laboratories, complex procedures, *etc.* Sites eligible for audit may include central laboratories, sub-contracted facilities, farms, universities, veterinary practices, contract archiving facilities, *etc.*

Quality assurance SOPs will normally include when and how site audits will be performed. For example for multi-site studies, there can be guidance that a minimum of 20% of sites must be audited. Not all phases of a study are possible or even desirable to audit and based on SOP requirements, the study type, site(s), Investigator and Monitor, the auditing team or auditor with support as required will need to decide what is essential, feasible and practical.

Duplication of the Monitor function who should ensure quality control of the sites and will sign a compliance statement at the end of the study should be avoided. Generally, what is audited in a clinical study site audit covers the monitoring competency.

The auditor will look for evidence of adherence to the following:

- Study protocol
- SOPs
- Personnel/facility/equipment requirements
- Appropriate governmental regulations and guidelines
- Contract agreements
- Common sense.

A facility audit should focus on the facility's operations that are used in support of the study protocol implementation, including personnel, equipment and procedures. The audit will normally include a review of monitoring techniques, computer systems used for handling documents and data, and a comparison of a portion of the CRFs against requirements and the protocol.

The following activities should be considered for assessment in addition to study-specific issues:

- Personnel records: check if qualifications and training of personnel are suitable for performing study tasks, check the site reporting structure – organisational chart and job-descriptions if available. Ensure that back up personnel, for example, veterinary surgeons that maybe called for in case of an emergency, have been trained and understand the requirements of both data collection and study design/withdrawal criteria. Visit reports and contact records can be checked to assess if the Monitor has addressed this.
- Protocol compliance
  - Are procedures being followed
  - Are deviations and amendments documented and notes to file written up to clarify where required.
- Equipment: look for evidence of suitability and maintenance/calibration records.
- Storage procedures and facilities for data and records: secure storage of documents during the study as well as suitable post-study archiving requirements can be reviewed if suitable.
- Check correct and secure storage of investigational medicinal products and appropriate documentation including labelling, drug receipt and accountability records, – drug disposition may be available when treatment regimens have been completed at the time of site audit. IVP handling and safety instructions should be available.
  - Storage should be secure, with limited access, in compliance with storage conditions with evidence of monitoring thereof, check if distribution and tracking is adequate.
- Check Animal facilities and operations.
- Sample handling/appropriate storage/trace ability.

Many problems arise due to errors in sample trace ability or faults due to inappropriate labelling storage of specimens after collection or delivery at the laboratory and during transport. Examples are identification of samples that need refrigeration with non-waterproof ink may become illegible, milk samples not kept appropriately refrigerated either after collection or transport show exaggerated bacterial growth, missing links between animal id and the corresponding laboratory code for the specimen, *etc.* Therefore, auditors should consider this to be a main inspection area to ensure that adequate systems and checks are in place. This includes the systems in place for sample

collection, labelling and identification, transport and storage both at the study site and the analytical facility.

- Is documentation up to date and complete.
- Are communication logs complete and consistent.
- Raw data:
  - Raw data forms the base line information to substantiate any claims made in study reports or registration dossiers. Checks in this area cannot be left out, and Monitor contact records can be checked to ensure that the Monitor has performed the required quality control in this area. QA can perform spot checks and/or observe ongoing data recording at the study-phase visited to ensure that proper data collection techniques are applied: check data for completeness; are any missing data explained, are corrections fully explained and clear, dates and accountability of recordings: who did what and when.
- Systems audits: Documentation to confirm any system has been checked for operational accuracy and reliability. Ensure back ups are available in case required.
- Analytical data
- Ensure archiving facilities are available and adequate.

To get the most benefit from audits and their results, personnel interactions between auditee and auditor are paramount to achieve maximum follow-up and improvement of processes for future studies. This is particularly relevant to AH field studies where experience of study personnel being audited is still limited and people usually do not yet know what to expect.

Good communication processes should be in place from the start. The site audited is best informed of what a site audit will entail prior to acceptance of the study and budget preparation. The Monitor can introduce the auditor or auditing team and preferably an audit agenda is sent to the site prior to the event to allow for the necessary time, documents and personnel to be available. An opening meeting should be arranged to further clarify the scope and plan of the site audit.

To ensure consistency and completeness of the audit, but also to increase objectivity and transparency, the use of audit SOPs are very important. Checklists produced by the auditing team can help with this, and to open them to the auditee will help them in their preparation to anticipate key areas and facilitate communication regarding audit findings.

A closing meeting should be held to discuss audit findings, both positive and factual.

Maximum effort should be made to ensure that any feedback on observations of non-compliance or suggestions for system improvement is performed in a positive way and that good relations are always maintained.

An audit report is normally issued to the Monitor and management, not necessarily to the site audited.

**25.5.3.4 Study Audits – Reporting Phase.** Guidance is given in the VICH GCP document that study documentation should be audited consistent with well recognised and accepted principles of QA and that the auditor should prepare a report, which certifies that the audit was conducted, and describing the auditing process (VICH GCP 8.1.2). It's the sponsor's responsibility to provide a final study report (FSR) for any study in which an animal has been treated with an investigational veterinary product whether or not the study has been completed as planned.

During the reporting phase, an auditor has the opportunity to assess all study activities implemented, including study management and monitoring, raw data and documentation data management and query resolution, and of course the report itself.



Normally, what is audited in the reporting phase covers the data, documentation and the report.

The type and degree of audit may vary depending on the systems in place, QA involvement earlier in the study. The critical status of the data (pivotal *vs.* supportive), the complexity of the study, the experience of the study personnel, *etc.* may also impact on this.

Timing of the report audit needs careful consideration and will normally be laid out in the SOPs. Too early and any changes made after the audit was conducted can introduce new errors, too late – after the report is signed off – and a report amendment may be required which, in turn, should be subject to audit.

To gain time, final study close out audits can be split up into various stages. In this case clear SOPs are necessary to describe individual sign-off of various processes by the Monitor. To avoid QA being mixed up with QC, an audit should only be performed on a completed item. Data verification is normally the Monitor responsibility, a task that can be helped by various systems applications within data management and biometrics groups. The QA should examine and determine whether requirements were implemented and performed as such and report any non-compliance if any occurred. It is therefore necessary that data management and study file closure are completed or in case of the report, in its final draft stage prior to auditing. A sampling plan may be used or pro-rata checks performed as long as this is recorded.

**25.5.3.4.1 Final Study Report.** A final study report audit should examine whether:

- The report accurately describes the methods and procedures used.
- If the report is a true and complete representation of the raw data.
- The study documentation is complete and supports the information in the report.

VICH GCP gives guidance on relevant information that should be included in the final study report. This includes complete representation of study activities undertaken and required by protocol including any amendments and deviations and all study results. Report templates are normally available in sponsors SOPs and these can be checked for compliance with regulatory requirements during the QA SOP revision. The report then needs checking for SOP requirements. Any additional reports like laboratory or statistical reports should also be considered for audit.

The following checks or spot checks should be considered:

- Check compliance with the protocol and any amendments and deviations.
- Is there consistency with study documentation.
- Consistency within the report, including statistical reports or summaries, any laboratory reports or other reports relevant to the study.
- Assure consistency with the data: Compare the statistical summary and analysis required by the protocol to the statistical report and the final study report.
- Check SOP requirements like template unique study identifier and report version identifiers, authorship signatures and statements, report circulation requirements, *etc.*
- When the investigator is not an author of the study report, a signed and dated document should be provided by the investigator for inclusion in the report describing the documentation provided to the author(s) and attests to the accuracy and completeness of the study documentation.
- Does the report accurately describe what happened in the study?

**25.5.3.4.2 Data.** To ensure that the results reported are consistent with the data collected, the total process from data collected to completion of the statistical report should be covered. Which parts thereof are included in the study related audit will depend on the systems and procedures in place.

Normally, the raw data *vs.* the finalised and signed off computer data/statistical report are inspected. To avoid the QA auditor becoming part of the QC, 100 per cent data verification is



not recommended. Checks here are similar to raw data review during the in-life phase, to check that data was collected in compliance with requirements of being attributable, original, accurate, contemporaneous, legible and complete. Data should be recorded on pre-established forms or bound laboratory books. All data points required by the protocol including their units should be available and explanations of any missing or corrected data should be in place. Spot checks are performed to assess if the data verification was performed accurately. How much data is checked will normally be suggested in the sponsor's QA SOPs and may vary on the nature of the study, personnel experience, on the number of errors found, *etc.* When a certain error level is surpassed, the auditor can interrupt his/her audit until a re-check is performed and signed off by the responsible personnel.

In case electronic data capture was used, the electronic record is considered the raw data, and the system should be validated to ensure that the integrity of the data is assured. The use of electronic data capture is very unusual in animal health since the size of studies normally do not support the extra costs of the programming, validation, back-up and training requirements necessary to make this a successful and cost-effective exercise.

**25.5.3.4.3 Documentation.** The final report audit assesses that all required data and documentation is available and is consistent with the study report. VICH GCP includes a comprehensive checklist of the study documentation that is required which is normally represented in the sponsor SOPs with additions specific to sponsor's internal, procedural and protocol requirements.

Checks normally include the following:

- Is the original study protocol including amendments and deviations available and complete.
- Is there adequate documentation available to support requirements in the protocol and statements in the report.
- Is raw data including all case record forms complete: are all recordings of observations and assessments including analytical results available, and is any missing data explained.
  - Animal records include:
    - History-purchase.
    - Informed consent of the owner – signed prior to inclusion in the study.
    - Are inclusion criteria met, is exclusion and removal subsequent to inclusion and animal disposal documented – are all animals accounted for.
    - Randomisation and treatment group allocation.
    - Dosing records according to protocol instructions and including confirmation that blinding requirements were met.
    - Adverse event reporting: ensure documentation of first observations, veterinary reports and contact records to inform the sponsor is available and there is consistency between them, and with the report statements on this.
    - General animal health observations to ensure that animal welfare requirements were met during the study, veterinary reports and alternative treatment records.
    - Documentation on animal feed and water as required depending on the nature of the study, including analysis.
- Investigational veterinary product and control veterinary product(s)
  - Drug request memos or ordering forms, any receipts of purchase.
  - Is a certificate of analysis available and consistent with other documentation and the report?
  - Receipt by the investigator or allocated person in the study if this is required by blinding instructions.
  - Inventory of the number of vials, volume, number of tablets, *etc.* received+contemporary signature.

- Documentation of volume(s) used and the regimen and route of administration: dosing details.
- Volume and number of vials left over, including documentation of what was returned to the investigator (if relevant), and how much product, (*i.e.* complete unused vials, or partly used) that was returned to the sponsor or otherwise disposed of. Disposition records of both the investigational and control products must be available.
- Correct labelling – is a copy of the label available.
- Drug safety information should have been forwarded to the investigator by the sponsor for products that are not yet registered, including precautions, handling requirements instructions on treatments in case of AE, *etc.*
- Analytical records.
- Do lot numbers/expiry dates, *etc.* add up on all documentation.
- Notes to file or contact records should include details to confirm procedures that where required but not included by CRFs or SOP forms, are documented. For example, animal arrival on the farm, any pre-treatment requirements, like dehorning prior to study start, *etc.*
- Visit and contact records
  - Both Monitor and Investigator should keep records of all contacts made relating to the design, conduct documentation and reporting of the study.
  - Monitor visit reports: the monitor can use these records to confirm that he has performed his monitoring responsibilities, for example, during the pre-study site visit to confirm that the investigator and staff have sufficient time to devote to the study and that the site is suitable, to confirm that the staff is adequately informed, confirmation that he/she has visited the investigator and study sites with sufficient frequency, *etc.*
  - Do visit and contact records match details in the report regarding the monitoring of visits.
- Sufficient information to document that the facility and equipment were appropriate to ensure that valid study results were obtained should be included and signed by the investigator where necessary.
  - Are archiving requirements covered; Sponsor SOPs will normally address how best to deal with study documentation archived with the investigator and at the sponsor's archives.

## 25.6 REPORTING OF AUDIT FINDINGS

Quality assurance SOPs should include details of how to report audit findings, to whom these should be reported and how follow-up and clearance of findings should be performed.

In general, findings are usually discussed prior to report issue with the auditee to ensure there are no misunderstandings or misinterpretations.

Findings and clearance of findings are recorded in the audit report, which should be signed by relevant parties and archived both for future reference and in case authorities would request to inspect these.

The following should be considered for inclusion in the audit report: personnel involved in the audit, scope and objective of the audit, venue/facility or documents audited, time point/phase of the study audited, reference documents used, audit findings, sign off by auditor, distribution and instructions for follow-up, responses and appropriate sign off.

The monitor and his management are usually the appropriate recipients to deal with follow-up. To help them focus during and make long-term assessment of improvement of compliance easier, classification according to severity/compliance status of the findings can be added to the audit report. To maximise benefit of the auditing process, findings can be categorised and summarised to allow for metrics and trend analysis to provide a clear view on status of compliance and identify opportunities for process improvement and training requirements.

In case significant deviations in a clinical investigation are observed, these should be brought to the attention of relevant management immediately. Some examples where this is the case include:

- Inadequate justification of suitable personnel training and qualifications
- Inadequate informed consent of the animal owner
- Failure to follow the protocol without adequate followup.
- Unreliable or inaccurate data
- Failure to maintain adequate drug accountability records
- Failure to account for all animals included in the study
- Failure to report adverse events.
- Inadequate control of products from animals treated with an investigational veterinary product.

Comments and corrective actions performed should be noted and signed and returned within the timeframe set out in SOP requirements.

## **25.7 AUDIT CERTIFICATE**

After audit closeout, an audit certificate for a study can be issued. This should include essential information like: the study identifier, the study procedures audited, auditing procedures followed, and the audit dates. Appropriate archiving of audit reports and related documentation (like completed checklists) should be assured and separate from study documentation.

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## **Part 3: Good Manufacturing Practice**



## Introduction: Good Manufacturing Practice

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*“Simply put, GMP is the means by which the patient gets the medicine that he or she expects – and nothing else.” — Anon.*

### 26.1 INTRODUCTION

It is generally accepted within the pharmaceutical industry that a system of control is essential to ensure that medicinal products are manufactured to required standards. The term good manufacturing practice (GMP) is universally used to describe the system or systems upon which this assurance is based.

GMP is applied, regulated and controlled in different ways across the Globe. Within the United States of America GMP is described in the Code of Federal Regulations (CFR) in a surprisingly short series of paragraphs commonly referred to as “the CFRs.”<sup>1</sup> The USA also adds the word “current” and thus abbreviates the term to cGMP. Although the CFRs are apparently written as rigid mandatory regulations, the US regulatory agency, the Food and Drug Administration (FDA) expects industry to constantly improve standards through advanced technology by using the FDA’s guidance documents or by following case law. A particularly useful way to sense the FDA’s current thinking on standards within the industry and how they should change is by reading the “warning letters” issued to companies whose operations fall short of expectations, which are published in a redacted form on its website.

At the time of writing the FDA has issued a major report detailing a revised approach to the application of GMP in the 21st century, which it considers should be based on a sound quality system but also encompass comprehensive risk assessment at each point of the process.<sup>2</sup>

Within the European Union (EU), GMP is imposed by two Directives which state that manufacturers of human and veterinary medicinal products must carry it out.<sup>3,4</sup> Two further Directives lay down the principles and guidelines of GMP<sup>5,6</sup> while a fifth imposes GMP on the manufacturer of an investigational medicinal product (IMP).<sup>7</sup>

The principles of GMP expressed in Directives 2003/94/EC and 91/412/EEC are brief legal statements of what GMP actually is which should be read and followed with care by the manufacturer (As 91/356/EEC the human GMP Directive was almost identical to the veterinary version, simply being a legal nicety to separate human and veterinary legislation. The recent requirements for GMP of IMPs forced additions to the Articles and repeal of the original



Directive). Nevertheless, those responsible for the regulation of medicinal products within the EU recognised that the industry needed more detail to help interpretation. The Directives make provision for detailed guidelines to be published to which manufacturers and “agents of competent authorities” (regulatory bodies of Member States) should refer.<sup>8</sup> (These detailed guidelines will hereinafter be referred to as the “Guide to GMP”).

Other countries or trading blocks have similar provisions for their own interpretations of GMP. Since the USA and Europe host a massive concentration of the pharmaceutical industry (and buy a lot of its products) this chapter will describe the interpretations of GMP with respect to those two systems but it is reasonable to assume there are no major conflicts of interpretation with other systems.

### 26.1.1 Why is Good Manufacturing Practice Required?

Medicines are required to meet the criteria of safety, efficacy and quality before they are granted an authorisation for manufacture and sale. The first criterion is examined during the application process when a balance must be struck between safety and the product’s clinical use. Simply put, will the product harm the patient more than the illness itself? Efficacy is shown by extensive clinical trials (Part 1). Will the product actually treat or alleviate the condition for which it is intended? Quality is determined by the total of the product formulation and design, its ingredients and packaging, the way the product is put together, the environment while it was manufactured and manner of storage during its lifetime. If the formulators’ vision for the product is to be maintained consistently from batch to batch and dose-to-dose, the manufacturer must have suitable controls to maintain quality.

If the complex set of operations necessary to manufacture and pack medicinal products is considered, the need for control becomes obvious. Raw materials are purchased, tested, stored, dispensed (measured or weighed) and put together by some means to provide a product which must be tested then packaged using components which have usually been obtained from another party. Added to this are the complications of monitoring the environment to which the product is exposed, taking suitable samples and checking the series of records for each batch of product. Manufacturing and testing equipment must be qualified, maintained and calibrated. All those involved in the process must be suitably qualified and trained according to the job they have to do and the responsibilities they hold.

Even in the smallest of facilities where simple products are manufactured there is the opportunity for operations to fail, due to human error, equipment breakdown or just occasionally sheer bad luck. When this happens, the systems in place must ensure the product will not reach the patient without a full evaluation to confirm it meets its quality requirements.

An attractive but unsafe way to determine quality is to take samples and carry out laboratory testing. If the sample fails to meet the required specification then it might show that something has occurred during the manufacturing process. If the sample meets the specification then it is only an indication but not an absolute certainty that the remainder of the batch is satisfactory. To be sure every dose is satisfactory means testing every dose. Obviously that is not possible because to test every single dose using conventional analytical methods would destroy the whole batch. Regulators and industry alike have long recognised that relying on sample results is fallacious. Thus, assurance of quality through GMP is the accepted alternative.

### 26.1.2 What is Good Manufacturing Practice?

The definition of GMP found in the European Directives<sup>5,6</sup> is:

*“... the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.”*

**Table 1** Section and chapter headings of the CFRs and the Guide to GMP

<i>USA code of Federal Regulations Part 211</i>	<i>Guide to good manufacturing practice</i>
Organisation and personnel	Quality management
Buildings and facilities	Personnel
Equipment	Premises and equipment
	Documentation
Control of components and drug product containers and closures	
Production and process controls	Production
Packaging and labelling control	
Holding and distribution	
Laboratory controls	Quality control
	Contract manufacture and analysis
	Complaints and product recall
	Self-inspection
Returned and salvaged drug products	

The same Directives define pharmaceutical quality assurance as:

*“... the sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use.”*

While there is no definition given in the USA CFRs it seems to be an assumption that GMP (or more correctly, cGMP) is the total application of the regulations laid down, for in the absence of conformance with any one of them, the product is considered to be “adulterated”.<sup>9</sup>

Official definitions are all very well for legal purposes but they give no clear indication of what is actually involved in the implementation or application of GMP. On that score there is no shortage of information for the manufacturer. The regulations and guidance documents lay down only the primary expectations.

Table 1 provides a comparison between the contents of the CFRs and the Guide to GMP. It is clear that the USA approach is more specific in detail than the European document although each regulatory authority effectively covers all areas in some way, for example the specific requirements for tamper-evident packaging found in the CFRs are imposed by other regulations within Europe.

Additional guidance for specific products, or for areas of interest demanding detailed guidance from the regulators, is provided in a series of Annexes to the Guide to GMP. The FDA also publishes “Guidance for Industry” documents, which spell out detailed requirements on specific manufacturing situations. Information on how a regulator might treat a particular aspect is given in the FDA’s specific “Inspection Guides” intended as aids to its investigators. Inspectors in the rest of the world turn to the PIC/S guidance and recommendation documents for inspectors.<sup>10</sup>

Thus, there is no shortage of regulations, official guidance and advice on GMP although the sheer volume seems overwhelming to the industry initiate. For clarification it is useful to refer to the Guide to GMP and examine each of its chapters in turn, illustrated by examples both of good practice and what happens when it is not followed.

## 26.2 ELEMENTS OF GOOD MANUFACTURING PRACTICE

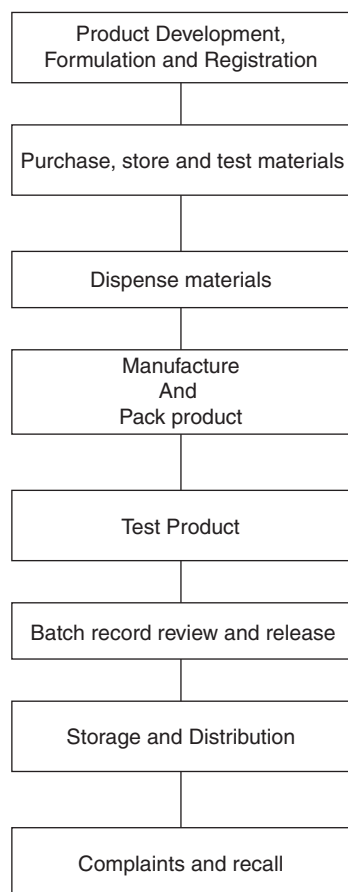
The nine chapters in the Guide to GMP cover all the elements involved within the pharmaceutical manufacturing operation. Some clearly overlap or cover identical requirements to the CFRs. Others contain some aspects of the CFR expectations without the precision of the US regulations. The imprecision of the Guide frustrates some but is not surprising. It is intended to cover the full

spectrum of the industry, from complex and lengthy biotechnical operations, to simple, rapid batch manufacturing. It must also be interpreted within each of the Member States of the EU, which by no means resembles the federal nature of the USA. In this way each manufacturer can ensure compliance while being able to manage operations in a flexible way.

### 26.2.1 Quality Management

Within the first principle of the first chapter on GMP is the requirement for the holder of a manufacturing authorisation to have a “comprehensively designed and correctly implemented system of Quality Assurance (QA) incorporating GMP and thus quality control (QC). It should be fully documented and its effectiveness monitored.” The QA system is expected to cover aspects even from the design through to distribution and, if it becomes necessary, recall of the product. A quality system must set out the roles and responsibilities of those persons involved.

How does one define a QA system? In setting up a manufacturing site the first step should be to map out the process. The basic elements of such a map are shown in Figure 1, but it omits areas of detail. It is not hard to envisage the many additional processes that must be added to each basic block. For example, appropriate qualified personnel must be recruited and trained for each job, equipment purchased, installed and qualified and maintained and calibrated properly. Processes require scale-up from development to full size and must be validated.



**Figure 1** Basic steps in the pharmaceutical manufacturing process

Quality management systems are discussed elsewhere in this book (Chapter 40). However, the general design of such systems tends to be common. A set of top-level statements of policy sets out management intent on key areas of the manufacturing process. A second level series of guidance documents expands on how the intent is to be turned into practice. Third and fourth tier documents set out operation procedures in detail and provide records of operations and results.

The objective of the QA system is to ensure that decisions are not made on an ad hoc day-to-day basis, depending on circumstances or urgency. Decisions should, in effect be made by the system itself. Management's role is to monitor that the system operates satisfactorily and will maintain control of the pharmaceutical manufacturing operations.

A useful example is the way that Change Control should be managed. The manufacturer has an obligation to make the medicinal product according to its marketing authorisation and must not deviate from it unless a variation is submitted to the appropriate authority and approval has been received (various authorities differ in the extent and manner of submissions of variations before approval is given but the principle remains the same). Without procedures underwritten by clear policy from management, changes, which are not reviewed by appropriate people and which are not authorised, can rapidly shift compliance to non-compliance.

*Example 1: It is tempting for the purchasing department to buy-in a raw material from a less expensive source and to persuade the laboratory to test and approve it. Production may find that material from the new source requires a change to the manufacturing process to achieve the product specification. In achieving one specification it might lose control over another—hardness of a tablet at the expense of thickness is a good example. The thicker tablet does not fit its blister pack quite so well, leading to a stability problem and a shorter shelf life.*

*Example 2: The site laboratory suffers a breakdown of an analytical instrument. It conveniently finds a laboratory within another company close by with a similar instrument and arranges for the samples to be tested there. This second laboratory is not listed on the company's manufacturing authorisation as an alternative testing site.*

The company policy on adherence to the marketing and manufacturing authorisations should be clear. If a change-control system had been in place which required review and approval by all interested parties, backed up by submission to the regulatory authority, then the loss of control shown by these examples would not happen.

### 26.2.2 Personnel

If there is one area of adherence to GMP that can make or break a pharmaceutical company it is in relation to the people it recruits, trains and develops. The Guide to GMP requires "an adequate number of personnel with the necessary qualifications and practical experience." It is up to the manufacturer to decide what each of these adjectives mean in relation to the operations in question but it is not hard to envisage that each one can lead to animated discussion!

Particular requirements are quite clear. There must be an organisation chart and there must be two key personnel, the Head of Quality Control (QC) and the Head of Production, who must be independent from each other. Under European law there must also be a third individual known as the Qualified Person (QP), unless one of the first two can also act in this capacity.

It is worth noting here that the CFRs do not demand named individuals but do require a "QC unit". In many recent (1998–2003) warning letters the FDA has cited the absence of a quality unit as the main reason why a company has failed to meet GMP requirements. It must be assumed that if there is a "QC unit" there must be someone at the head of it, whatever their title.

The Heads of Production and QC have individual and shared responsibilities which can be summarised as follows:

The Head of the Production Department should:

- ensure products are produced and stored correctly
- approve instructions relating to production and ensure strict implementation
- ensure production records are evaluated and signed
- check maintenance
- ensure validations are done
- ensure training is carried out.

The Head of the QC Department should:

- approve or reject materials and products
- evaluate batch records
- ensure testing is carried out
- approve specifications and other QC procedures
- approve and monitor contract analysts
- check maintenance of his department
- ensure validations are done
- ensure training is carried out.

Shared responsibilities include:

- authorisation of procedures
- monitoring and control of the environment
- hygiene
- process validation
- training
- approval and monitoring of suppliers
- approval and monitoring of contract manufacturers
- designation and monitoring of storage conditions
- retention of records
- monitoring compliance to GMP
- inspection, investigation and taking of samples to monitor factors which may affect product quality.

It is well worth noting that training figures both as an individual and shared responsibility for the named Heads, emphasising the importance of this topic. Untrained personnel operating within the manufacturing, packaging and testing environment are dangerous, since they can act in an unaware, albeit well-meaning way.

*Example 3: An untrained packaging operator picked up an apparently good pack of product from the floor and put it back on the nearest packaging line, where it was assembled with others. The pack actually came from an adjacent line packing product with the same name but of a higher strength. Because the high strength pack was collated amongst others of low strength it went unnoticed in the dispensary and a patient suffered serious side effects.*

*Example 4: An untrained dispensary operator did not appreciate the difference between two materials which were identical except for a different suffix on the label which indicated the viscosity grade. The material was used in a tablet granulation which seriously affected dissolution of the product in vivo.*

These are typical examples of actions carried out by individuals who were unaware of the serious consequences of simple mix-ups. Proper and thorough training, repeated and updated on a regular basis, is essential within the pharmaceutical-production environment. Such training must include all those who work directly on production, packaging or testing but attention should also be given to those whose activities take them into the production or testing areas on an occasional basis, for example maintenance engineers. Office-based personnel who work in purchasing, human resources and finance should be taught which areas they can access without an escort, if any, what to wear and how to behave when in them.

Key personnel and those in responsible positions should have appropriate qualifications to understand the theoretical basis of the activities they carry out. An important example is the facility that manufactures sterile products. It should be managed and supervised by graduates with a microbiology or biology qualification who appreciate the very special requirements demanded. Some authorities require any aspect of pharmaceutical production to be supervised by a pharmacist.

### 26.2.3 Premises and Equipment

**26.2.3.1 Premises.** As a general rule, production facilities must be located in an area which will not adversely affect the operations carried out within. The design and construction must also suit the activities. However, often the managers of a pharmaceutical factory are faced with a “*fait accompli*” when it comes to the facilities in which they operate. The operation may have started many years before when the facility was newly built but since then the products handled within and the activities of any factories surrounding the site may have changed dramatically. Nevertheless the managers have a responsibility to develop the facilities, upgrade and adapt them as required, to accommodate the changing circumstances. If the external environment becomes contrary to the operations, for example in the worst case, next to a land-fill site for waste and rubbish which attracts vermin and flies, there may be little choice but to move. It may be possible in less serious situations to ensure that the external activities will not affect the products. In any case there is an obligation to keep out insects and other animals and to monitor the effectiveness of any programme to do that.

It is an expectation of GMP to maintain premises and to keep them clean and hygienic. It therefore follows that they should be appropriately lit with temperature and humidity controls to maintain suitable working conditions which permit these requirements.

Operations which might cause serious contamination of medicinal products with toxic materials, are not permitted. Thus production and storage of non-medicinal products and especially pesticides and herbicides are not allowed in the same facility although certain cosmetics may be (Note, however, that in the case of veterinary ectoparasiticides it is permitted to manufacture in pesticide specific areas in the same premises as other veterinary products).<sup>11</sup> It is expected that highly sensitising materials such as penicillins are produced and handled in separate facilities altogether. Other products, including certain other antibiotics, hormones, cytotoxics, and other highly active drugs should have dedicated areas although production on a campaign basis can be authorised. If so, validation of the cleaning and changeover procedures must be thorough.

An aspect which cannot be over-emphasised for any facilities but especially in storage, production and laboratory areas, is the provision of sufficient space. Lack of space causes many examples of cross contamination, mix-ups and deterioration of product or packaging.

*Example 5: During a period of intense production activity in one facility, storage space within the warehouse came under pressure. As a consequence the general rule of “one item – one pallet” was ignored and boxes of leaflets for two different products were stored next to each other on the same pallet. The wrong boxes were included in a consignment to the packaging line and the*



*leaflets packed in the product. Luckily the mistake was spotted in a pharmacy but the subsequent recall was very embarrassing for the company.*

The materials of construction and finish for any area must be appropriate to the activities carried on within. Surfaces must be smooth to allow cleaning operations to be effective but must also be of suitable materials so as not to shed particles or contaminate the product. Floor surfaces in particular must be sound and capable of withstanding vigorous cleaning agents. There are many proprietary materials for all surfaces and the manufacturer is well advised to search extensively for suitable items and to seek advice from other manufacturing sites as to their experience with various options.

Personnel should be provided with separate facilities for rest and refreshment. The wearing of working clothes in refreshment areas should be avoided if at all possible and certainly should be forbidden where facilities are shared with non-production personnel and visitors. Suitable areas should be provided for personnel for changing clothes and for washing and toilets.

**26.2.3.2 Equipment.** The Guide to GMP is surprisingly short in its treatment of equipment. This is remarkable when considering the effect of improper, poorly maintained and uncalibrated equipment on the quality of the final product. The range of processes covered by pharmaceutical equipment is enormous, from simple measurements through complex processing operations to huge packaging lines. Additionally, equipment is often serviced not by the production department that uses it but by an engineering department reporting separately to senior management. A particular aspect required of the Quality System is that such relationships are well organised and properly managed. Repair and maintenance activities result in engineering operatives moving from area to area with the potential for cross-contamination from their work clothes.

The first requirement of a piece of equipment is that it will not harm the product exposed to it and should do the job it is intended for. Thus it should be constructed of suitable materials. Those parts coming into contact with the product should not react with it nor release or absorb any materials. If plastics are used this may be of special importance.

Nowadays, it is a generally expected requirement of GMP that all pieces of equipment that affect quality will be subject to a systematic maintenance programme. Aspects of such a programme which ensure it will be effective are:

- a master list of equipment
- designation of quality critical and non-critical equipment
- a schedule of maintenance for each piece which specifies among other things which parts may be changed without seeking further authority
- procedures to specify action if the maintenance interval is delayed or missed altogether
- records of maintenance showing any parts that were changed or adjustments made
- procedures to remove any piece of equipment which becomes defective, redundant or obsolete.

*Example 6: A maintenance engineer was called to replace an 'O' ring in the seal of a valve. The material was supposed to be black neoprene, deliberately chosen so that any particulates it released would be immediately visible. The engineer did not have a similar replacement and inserted a white nylon ring instead. White particulates were later found in an injectable product produced with the equipment.*

It is expected that measuring equipment will be subject to a planned calibration programme with similar aspects to the above.

Additionally there must be strict procedures to be followed in the event that:

- a calibration interval is delayed or missed
- the instrument is found to be outside its calibrated parameters.



In the last case any action should include a review of all those batches of product which might have been affected by an incorrect measurement.

Each piece of equipment should have a log book(s) or similar record(s) which records all maintenance, calibration and cleaning carried.

#### 26.2.4 Documentation

The quality of a company's documentation system reveals the quality of its Quality Assurance System. Documents should be clearly written, well laid out, easy to follow and with sufficient room to fill in information and results where needed. Those who manage the documentation system must ensure that documents are maintained up-to-date and that only current documents are made available to the operations. It is especially important that necessary changes to documents can be carried out within a short time. Needless bureaucracy that hinders and delays corrections to typographical errors or obvious mistakes leads to frustrations and continued use of the incorrect document, probably with hand-written amendments. This effect, which is frequently found when document management is poorly controlled or left to junior staff, is a significant indicator of a weak QA system, not as some would have it, the opposite.

The Guide to GMP sets out the minimum requirements for various documents expected to be found in the manufacturing site. The four basic types of document are stated to be Specifications, Manufacturing Formula, processing and packaging instructions, Procedures (Chapter 27) and Records. The latter is further subdivided into records of Receipt, Sampling, Testing and Other procedures including for example Validation, Pest Control and Recalls. Figure 1 suggests that there must be many other examples within the system. It is also a reminder that a document system should be designed as part of the QA system. Proper design leads to minimisation of the number and type of documents used. An example of poor design is the proliferation of similar procedures covering minor differences.

*Example 7: A company had separate procedures to cover each type of change within its operations e.g. materials, processes, packaging and test methods. The evaluation of each change and the form used to control them was actually almost identical. This system also failed to recognise that many related minor changes actually made one critical change. By consolidating the separate procedures the company eliminated many pages of repetitive procedures and related changes were properly evaluated for their overall effect on the quality of the product.*

Thus a valuable action by auditors is to ask for a list of standard operation procedures, choose those which seem similar to each other and on examination, compare them for similarities or as more often happens, conflicts between identical activities in different areas.

#### 26.2.5 Production

**26.2.5.1 General.** It is axiomatic that production operations must be performed and supervised by competent, suitably qualified and trained people. It is also a basic, maybe obvious but not always followed expectation that all operations will be carried out in accordance with written procedures (Chapter 27).

**26.2.5.2 Prevention of Cross-Contamination in Production.** Manufacturers should be aware of the risks of contamination of starting materials or products by another material or product, potentially with harmful effect to the patient. Particular hazards are present in facilities handling highly sensitising materials, biologicals, living organisms, hormones, cytotoxics and other highly active materials. Injectable products, those administered in large doses or over a long period of time, present a particular risk if contaminated.

Thus the manufacturer should make efforts to avoid cross-contamination. It may be possible to do this effectively in a number of ways, depending on the circumstances and the products involved. Total segregation of facilities is an obvious but expensive option, which may be unavoidable in certain instances. Lesser options include the provision of air-locks between areas at risk or providing independent air-handling units. Organisational arrangements such as ensuring that one person does not work on different products without a change of clothing may be effective. In any case, cleaning, decontamination and monitoring procedures should have demonstrated effectiveness. Test methods used for residues should be evaluated for their ability to detect the very low levels that may be present.

**26.2.5.3 Validation.** Significant additional guidance on validation was introduced by the relatively recent inclusion of Annex 15 in the Guide to GMP. Nevertheless some general principles are worth repeating here:

- all manufacturing processes should be validated
- significant amendments to processes should undergo evaluation to check whether re-validation is necessary
- all processes and procedures should undergo periodic re-validation to ensure they remain capable of achieving the intended results.

Validation activities should be carefully recorded as this record is useful in examining the cause of problems and deviations that occur when the process is used repeatedly.

**26.2.5.4 Starting Materials.** Since starting materials are fundamental to the quality of the final product the manufacturer should ensure that procedures for selection and control of suppliers are sound. An “approved suppliers list” should be maintained by the quality unit. This should be accessible to all those who handle materials or who deal with supplies such as warehouse personnel, sampling and testing staff and purchasing. Additions or deletions to the list should be controlled by the company change control procedure. Materials received from unauthorised suppliers should be returned or quarantined pending formal approval.

Materials receiving procedures should ensure that each container is checked for proper labelled identity and is of the material ordered. If several batches of the same material are received together they must be separated and controlled by internal company batch numbers. Each container should be formally sampled and tested to ensure the identity of the contents, unless an evaluation of the suppliers quality system has shown this to be unnecessary.

It is expected that materials will be properly stored, free from the possibility of mix-up and contamination and in a suitable storage area which is temperature and if needed, humidity controlled. A system of re-evaluation should be in place with an assigned retest or expiry date to each batch of material.

Only materials which have been released by QC should be used. They should be dispensed in designated areas by properly trained operators (see example 4 above), and an independent check of the identity and weight or volume must be made. They must be labelled properly.

*Controversy exists with respect to the definition of “an independent check.” Whilst a first interpretation might be that a second person is required most European authorities would probably accept a separate check by bar code reading equipment backed up by a printout from the weighing equipment. The CFRs clearly require a second person.*<sup>12</sup>

**26.2.5.5 Processing Operations: Intermediate and Bulk Products (Chapter 28).** Basic principles of production not included elsewhere are:

- the work area must be free from materials, products, residues or documents that are not related to the current operation

- environmental conditions should be suitable and should be monitored. If intermediate or bulk products are to be stored, even for a short time, they should be kept under appropriate conditions
- significant deviations from expected yield should be recorded and investigated. It is up to the manufacturer to define what is significant but this is often apparent by examining trends after several batches have been made.

An area not well covered by GMP guidelines is the requirement for a procedure to control and investigate any deviations from the standard procedure (Chapter 27). This is an important topic for the manufacturer to cover because deviations often require urgent evaluation and decision-making, unlike controlled changes, which more often than not can be evaluated in a less frenetic atmosphere. The starting point for a deviation procedure must of course be the assumption that operator training clearly instructs that no deviation from the laid-down process can be allowed. However, mistakes do occur. In addition equipment breaks down, power cuts happen which are outside anyone's control. All of these potential events need some thought on how they will be evaluated. A sound deviations procedure is most important in this respect.

**26.2.5.6 Packaging Materials.** Because packaging problems are the most frequent cause of product recalls worldwide, it is not surprising that no less attention must be given to their source and control than to raw materials. Similar attention to selection and monitoring of suppliers is required. It should be remembered that suppliers of printed packaging and manufacturers of packaging items such as bottles, closures and blister foils more often than not supply many other non-medicine industries. The consequences of label mix-ups, or poor closure/bottle fitting may not be so "exciting" to those outside the pharmaceutical industry.

**26.2.5.7 Packaging Operations.** It is at the packaging stage that the opportunity for major errors really presents itself. All those involved within packaging operations should be vigilant to the possibilities of mix-ups of product, labels and leaflets and other printed matter. Packaging areas are usually very busy with several lines operating side by side, albeit suitably separated. Packaging operators and in particular engineering fitters move from line to line as production requirements dictate. These movements carry the potential for small items such as tablets, capsules, ampoules and vials to be carried accidentally from one line to another. Most packaging lines nowadays use self-adhesive labels supplied on rolls, which minimise the likelihood of an odd label drifting about. Nevertheless, those who still use individually cut labels must be especially vigilant.

Thus procedures in the packaging area should control product and materials coming to the area from the stores. Operators must be trained to recognise subtle differences between similar products and packaging. Line clean-down and start-up procedures must ensure that residues of previous product and packaging are removed and checks made to ensure the line is clear.

During the packaging operations routine checks should be carried out to ensure that the integrity of the pack remains in control. Such checks include confirmation that overprinted information remains correct and legible, that labels, leaflets and cartons are of the correct identity and that closure and seal integrity is within the expected limits.

*Example 8: During a long packaging operation more labels were required. Labels for the product with the correct name but different strength were issued by the store. Because they arrived on the line at a shift change over they went unnoticed and part of the batch was distributed with incorrect labels.*

An important aspect of packaging is the reconciliation procedure after a batch is completed. Reconciliation must take into account both the product and packaging which was:

- sent to the line
- used in the pack

- lost during packaging
- left over.

Procedures should also be clear on what to do with the leftover product and packaging. Owing to the danger of mix-ups some companies do not return opened cartons of leaflets or printed items to the store. Any product left over may also be uneconomic to keep when the dangers of mix-ups are considered.

**26.2.5.8 *Finished Products (Chapter 28).*** Storage procedures should ensure that any finished product cannot be released for distribution until it has been released. At all times it should be stored under suitable conditions. Sometimes it is necessary to pack products at room temperature, which must then be cold stored to maintain shelf life. If that is the case, the maximum time allowed at room temperature should be stated.

**26.2.5.9 *Rejected, Recovered and Returned Materials.*** The careful control of rejected materials is paramount, especially if they are products from within the manufacturing site itself. They must be labelled properly and stored in a separated and designated area. Access to this area should be restricted.

Any reprocessing of a rejected product should be exceptional and requires full evaluation to ensure that the final quality of the product will not be affected. Recovery of products from batches which did conform to the required quality, requires prior approval within the marketing authorisation. Recovered material may require additional testing to confirm the quality.

## **26.2.6 Quality Control**

**26.2.6.1 *General.*** There is a fundamental requirement for the manufacturer to have a QC department that must be independent of all other departments. The continued use by all regulatory authorities of the term “QC” has changed the historic perception of this department, which must have authority for all decisions related to quality. Indeed, the Head of QC should be an authoritative figure, with the qualifications, training and experience necessary for the particular function (The responsibilities of this position were provided under “Personnel” above). Quality Control staff must also be allowed access to all production areas to allow sampling and investigation if required.

The QC department is also expected to establish, validate and implement all QC procedures, keep reference samples, ensure correct labelling, ensure stability monitoring and participate in complaints investigations. Most modern pharmaceutical organisations delegate these responsibilities to a department known as “Quality Assurance” but the independence from other departments must be maintained.

GMP emphasises that finished-product assessment is not simply a question of testing samples to see if they comply with a specification. All factors which might have an effect on quality must be taken into account, including environmental conditions, review of production and packaging records and examination of the finished pack.

**26.2.6.2 *Good Quality Control Laboratory Practice (GCLP) (Chapter 30).*** Good quality control laboratory practice is a subdivision of GMP related to proper organisation and management of the laboratory operations related to testing medicinal products. GCLP should be distinguished from good laboratory practice (GLP), which is a term formally reserved for the regulation of animal testing laboratories (Part 2).

A laboratory must have an appropriate documentation system. Since the activities should be governed by the operation of the quality system it follows that the documentation system should be

designed as part of the overall company system. This is often found not to be the case, leading to confusion of definitions and different levels of quality in documents between the GCLP system and the main GMP system.

Whatever the system, the QC department has a responsibility to store documents related to the quality of each batch produced. The minimum storage periods are set out as 1 year after the expiry date or, within the EU, 5 years after the certification by a QP. Such records should include all original data such as that found in laboratory notebooks.

Special attention should be drawn to the requirements for sampling. It is recognised that any sample, at best, can only give a snapshot of the quality of the whole batch. Thus samples should be taken with care using trained operators following clear procedures. Any ad hoc samples should be treated carefully, unless they have been taken using a preordained plan. Samples must be labelled with, as a minimum, the contents, batch number, date of sampling and some indication of the containers from which the samples have been drawn.

Reference samples of materials and finished product must be retained. In the case of finished product the minimum period is 1 year after the expiry date. Raw materials should be retained for 2 years after release of the last batch of product containing them. There are exemptions for raw materials which would be hazardous to keep or which are volatile. The size of all samples should permit at least one full set of tests to be carried out. In the case of finished products the manufacturer should ensure that the sample is not lost to retesting early on in the shelf life by retaining sufficient for several retests.

Analytical methods should be validated (Chapter 30) and in any case all tests should be carried out in accordance to the marketing authorisation. Subtle changes, which “improve” the methods, must be avoided unless properly authorised by the appropriate authorities.

*Example 9: An analyst adjusted the wavelength at which an HPLC method was carried out to obtain a sharper peak of the active ingredient. A related substance, not normally found in the product but which was quoted in the active ingredient specification, was missed because it did not absorb well at the new wavelength. This related substance was subsequently found during stability studies and the batch had to be recalled.*

The Guide to GMP lists the requirements for the test records<sup>13</sup> and specifies the minimum standards for laboratory reagents and glassware.

### 26.2.7 Contract Manufacture and Analysis

Many holders of marketing authorisations do not also hold a manufacturing authorisation. Even the holder of a manufacturing authorisation itself might require additional services to those which he can provide within his own organisation. The Guide to GMP provides a structure around which such arrangements should be made. It describes the role of the “Contract Giver”, that is someone who wants work carried out on his behalf; and the “Contract Acceptor” or the person who agrees to carry out that work.

Holders of marketing and manufacturing authorisations have responsibilities to ensure that any product is manufactured and tested according to the terms of the marketing authorisation. When such responsibilities are delegated it is vital that a written contract is drawn up between the parties, which clearly sets out who will discharge those responsibilities and how communication will occur.

Proper lines of communication are especially important with respect to approved changes to the formulation, process or tests. Additionally the responsibility for certification by the QP and product release must be clear.

The Contract Giver must be given access to the Contract Acceptor’s premises and any records related to the products. The Contract Acceptor must not engage in any activity detrimental to the contracted products.

It should be noted that contract facilities must be approved and included on the appropriate manufacturing and marketing authorisations. Contract laboratories are subject to regulatory inspection, whether they are part of an organisation which holds a manufacturing authorisation or not.

### 26.2.8 Complaints and Product Recall

**26.2.8.1 Complaints.** Manufacturers must have a written procedure for dealing with complaints and a responsible person should be designated to handle all complaints. This ensures that if a series of complaints is received related to the same product or a particular batch it is recognised as requiring serious attention immediately. If applicable, the QP must be made aware of all complaints since he or she might have to take the initiative to recall a batch of product.

The complaints procedure should ensure that a proper and timely investigation is carried out to determine the probable cause of any complaint and to decide if there is a serious defect. The consequences for other batches of the same product or for other products (*e.g.* in the case of a packaging defect or defect raw material) must be taken into account. The complaint procedure should also involve other departments and appropriate disciplines such as medical and regulatory affairs groups within the company, to provide an assessment of criticality.

**26.2.8.2 Recalls.** As in the case of complaints, there should be a written procedure that lays down the action to be taken in the event that a decision to recall a batch or batches of product has to be taken. A designated person should be responsible for co-ordinating the company's actions and for communicating with regulatory authorities.

Since any recall may require urgent and immediate action the procedure should be capable of operating at any time, including weekends and holidays. It is especially important that those who are in charge of the distribution records can be contacted and are capable of providing them at a moment's notice.

Most regulatory agencies have a specific department that must be notified in the event of a defective product which might be recalled or which is being recalled. The contact address and telephone and fax numbers should be included within the procedure and regularly checked to ensure it remains current.

Any products which are returned due to being recalled must be held in a separated and controlled location within the storage facility. They should be properly labelled as their status and destroyed as soon as possible after the recall is judged to be complete. The person responsible for the recall should issue a written report to include reconciliation, as far as possible.

The recall procedure should be evaluated on a regular basis for its effectiveness. This is often done by carrying out a "dummy" recall by choosing a batch and determining how rapidly information on its distribution can be gathered. The dummy run should also test the availability of key contacts and whether contacts are up-to-date. It is not sufficient to treat a real recall as this dummy test, since all the elements of the procedure might not have been tested.

### 26.2.9 Self-Inspection

The effectiveness and currency of the Quality System must be regularly evaluated by means of a self-inspection programme. Elements of a successful and effective programme are:

- a procedure for conducting self-inspections naming those who should carry them out. Preferably they should be carried out by an independent individual, accompanied by those responsible for the area under inspection
- a matrix of areas, systems, and facilities to be inspected against a planned schedule



- written reports with recommendations for improvement
- senior-management review of planned and completed corrections.

## 26.3 CONCLUSION

This chapter has summarised the requirements of GMP, mainly according to the expectations of the European Guide to GMP. The examples provided indicate the major defects that can occur due to apparently minor or simple actions by untrained or unthinking individuals. Detailed requirements for manufacturing controls on specific areas of production or specific types of products are found in the Annexes of the Guide to GMP, which should be consulted if applicable. The requirements for the GMP manufacture of IMP for clinical trials are detailed in Chapter 29.

GMP is an evolving and dynamic requirement. The community expects continuously improved assurance of safety and quality from its medicines. Practices which were acceptable even a few years ago are no longer satisfactory. The manufacturer and especially those responsible for the implementation and maintenance of GMP should constantly be aware of that.

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13. See ref. 8 at 6.17.





## CHAPTER 27

# Standard Operating Procedures

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## 27.1 INTRODUCTION

Standard operating procedures (SOPs) are occasionally seen as a burdensome requirement, a bureaucratic nuisance that must be complied with because of the good manufacturing practices (GMPs). Certainly, the creation and maintenance of an SOP system does require resources, but if written properly, and with an understanding of their purpose, then SOPs are vital documents in the effective and efficient running of a quality management system, as well as a key tool in ensuring GMP compliance.

This chapter first considers general aspects of an SOP system, and then suggests the areas and subjects for which SOPs might be required in a facility operating to GMP. Elements of the former have also been discussed in Chapter 3 but are worthy of emphasis in a GMP context.

## 27.2 WHAT IS AN SOP?

Any document giving written instructions of how to carry out a task (*e.g.* an SOP describing how raw materials are dealt with when delivered to the receiving dock of a warehouse), or describing a system (*e.g.* an SOP setting out the responsibilities of the Quality Assurance (QA) department) is, for the purposes of this chapter, and the GMPs, considered an SOP. A normal GMP quality system will also include other types of documents, such as policies (broad statements of organisation policy on a given topic), master formulae, manufacturing instructions, specifications for starting materials, intermediates and finished products, protocols (covering such activities as validation and stability studies), and, of course, records. However, the core of any GMP system is the SOPs. Sometimes, procedures for different areas of an organisation are given different names (*e.g.* top-level documents are SOPs, documents describing manufacturing operations are “Manufacturing Procedures”, QC activities are described in “Standard Analytical Procedures” and “Analytical Methods”, equipment calibration is covered by “Standard Calibration Procedures”, *etc.*). What these different types of instruction documents are called is really a matter of convenience for the organisation, but for the purpose of this chapter they are all referred to as SOPs. SOPs tell people what to do, and how to do it. This means that there are SOPs for tasks in the manufacture and testing of a pharmaceutical, SOPs for the cleaning of facilities and equipment, SOPs on training staff and SOPs on the SOP system itself. All of these SOPs have, of course, very different content, and are usually specific to one organisation, but certain key principles and processes apply to all SOPs.

### **27.3 LEVEL OF DETAIL IN SOPs**

Given the regulatory interest in SOPs, there is a temptation to have a small core of rather slim documents called SOPs, which are relatively short on detail so that non-compliance cannot easily arise. Sometimes there are other more detailed documents behind these to ensure consistency in carrying out the activity. However, no matter what they are called, a regulatory inspector will generally consider these supporting documents as part of the SOP system. If there are not supporting documents filling in the detail left out in slimmed-down SOPs, then the risk of divergent, and therefore non-compliant, activities is relatively great. It is therefore probably best to write complete SOPs, describing tasks in sufficient detail, although avoiding specifying things that do not really need to be rigidly controlled (see Chapter 3).

### **27.4 SIZE OF SOPs**

Is it better to describe all aspects of a particular topic in a single large SOP, or would it be better to have a separate SOP for each aspect? This is an impossible question to answer, both approaches have advantages and disadvantages as discussed in Chapter 3. Fully comprehensive SOPs have the advantage that all aspects are covered in a single document, so nothing is overlooked and there is little worry about the interfaces between different topics being confused. On the other hand, this can result in documents that are 20 or more pages long, which is very unwieldy. Shorter and more specific documents make reading and use of the SOP easier, but there are, necessarily, more SOPs which increases the administrative burden. There is no single answer, and even within a single system, there are probably circumstances where each approach is more appropriate. In general, however, SOPs above six or seven pages long tend to become difficult to use, as it is not always easy to identify where the required information is to be found.

### **27.5 PURPOSE OF SOPs**

The GMPs require that all instructions are in writing; SOPs, which as mentioned above, are written instruction documents, meet this requirement. The primary purpose of an SOP, however, is not simply to meet the requirement of the GMPs. Their purpose is to give instruction so that tasks are performed in a consistent way, and to be a basis for training staff in how a task is carried out. To allow this, an SOP must be clear, correct, complete, and up-to-date, and approved.

### **27.6 SOP CONTENT**

It is best if SOPs are all laid out according to a standard template, as this makes finding your way around the document easier. Each organisation has its own way of laying out documents, and no one way is correct. However, there are certain common features that should be included in every SOP format. These include the company name, a clear SOP title, an SOP number, and as SOPs are often amended, a version number. Every SOP has to have an effective date (a date from which it must be followed), and all the pages should be numbered (best done in the format “Page x of y” so that it is easy to establish that no pages are missing. When SOPs are amended, it is often valuable to have a brief summary of the changes (often called a History section) placed somewhere in the SOP, as a clear indication to users of what has been altered. Additionally, each SOP needs some way of indicating that it has been reviewed and is approved for use. Usually this is done by signature of one or more pages of the SOP by the author and by one or more people who are empowered to authorise use of the SOP within the organisation. All these elements should be described in an SOP or SOPs (see Section ‘Documentation’) later. However, the key component of

each SOP is its instructional or descriptive content. Each SOP should describe a connected set of activities. It should be stated who is responsible for carrying out each action described. SOPs should describe the activities to be followed in a clear stepwise fashion, and it is often easier for operators to follow if the SOP should be written in the active, rather than the passive, voice (“Do this” rather than “This should be done”).

## 27.7 SOP CREATION, APPROVAL AND DISTRIBUTION

The GMPs do not specify who should write SOPs, and technical writers are sometimes used. This can produce well-written documents that are not actually that useful, as they are not written from the viewpoint of the user. It is usually better that the SOP is drafted by someone with detailed knowledge of the activity that forms the SOP subject, as in this way the most meaningful, and useful, SOP will result. If necessary, a technical writer can support the person actually writing the document. A first draft should be produced in the organisation’s standard format, and should be circulated to the relevant staff, that is those who will use the document, and the group(s)’ supervisor(s). After all are agreed that the draft clearly, correctly and completely describes the desired operation, and that it interfaces properly with adjoining operations, with no overlaps, and no gaps. The reason for avoiding gaps between SOPs describing stages in a process is obvious, but overlaps can cause just as much trouble, for it is almost certain that if any activity is described twice in different SOPs, then over time, as the SOPs are amended, that the two descriptions will diverge. In addition, there is a risk that the activity described twice will be carried out twice; indeed, it should be if the overlapping SOPs are properly followed!

Once a final version has been agreed by the author and users, then it should be reviewed by the department manager(s) and by QA. They should signify their approval of the document by signing it, and of course, their signatures must be dated. It is important that all relevant managers review and approve the document, but only those relevant. Some inspectors have been known to identify the highest-ranking person on an SOP approval list and ask her/him technical questions about the SOP. People must not sign documents that they do not understand, and the reason for and meaning of their signature must be clear.

There are different schools of thought on where the signatures need to be placed. Some organisations require that every page is signed by one, if not all, of the people required to give approval. The basis for this is that it shows that every page has been read. Other organisations require only that a single page (often the front page) is signed by all relevant parties, and make it clear in their SOP on the approval of SOPs that a signature on one page signifies, among other things, that all the documents have been reviewed and approved. Yet another way is to collect the signatures on a separate form entirely. There is no correct way; the key point is to decide a system, describe it in an SOP and comply with it.

Standard operating procedures are of no value if they are not available to the people who carry out the task described, at the location where they are needed. It is not a requirement of GMP that staff must have the relevant SOP “open” in front of them when they carry out the specified task, but it certainly is a requirement that the relevant SOP is available at the point of use in case the operator wishes to consult it. Therefore, copies of the approved SOP have to be freely available at the point of use on and after the effective date. This is a specific Food and Drug Administration (FDA) requirement. Perhaps the simplest way to accomplish this is to issue paper copies, to individuals or departments, who are then responsible for looking after this copy. Alternatively, electronic systems can be used. These have the advantage that up-to-date copies can be available instantly anywhere there is a PC, but a way must be established of preventing the SOPs being modified (one way to do this is to use a system based on a package such as “Adobe Acrobat”, for example, Stellant Content Manager). Of course, this requires either that there is a computer or terminal

available at every potential point where an SOP might be used. This is not always easy to achieve. One way around this is to set up the electronic system so that copies of SOPs can be printed on demand. It would be extremely labour intensive to attempt to control the distribution of copies printed in this way, to record the names of everyone who printed any copy of an SOP, and to recall and reissue them all when the document is revised. Instead, it is more appropriate to configure the system to watermark or otherwise add to each copy printed the date of printing, and some limitation on the duration over which such a copy can be used. For example, the text could be “Valid on Date of Printing only” or “Only Valid until (Date)”. The system used by one of the authors allowed any SOP printed from the electronic distribution system to be used up to and including the following Sunday. New issues of SOPs were only made on Mondays.

One other problem with the distribution of paper copies, whether they are issued as controlled copies or printed electronically, is the use of paper in cleanrooms. Paper creates quite a lot of dust, and is also difficult to sanitise in a way that maintains the legibility of the text. One simple solution is to laminate the SOPs in clear plastic, which seals in the dust and also gives a surface that can be easily wiped with a wide range of disinfectants without physical damage.

Finally, in the spirit of making SOPs available at point of use, it is common to see parts of SOPs mounted on walls in the production area. Perhaps the most common instance is an extract of the SOP on cleanroom clothing, describing the changing into and out of cleanroom clothing, mounted on a changing room wall. This is very valuable, but it is important that this extract is part of the controlled SOP distribution system. It sometimes occurs that someone decides it would be useful to mount part of an SOP on a wall in this way. A partial copy is made and mounted. Because it is not part of the controlled distribution system, it does not get recalled when the SOP is updated (particularly if the section mounted on the wall is not changed). Because all the operators see this extract every day, it effectively becomes invisible, and its only when an inspector or an auditor comes around that the out-of-date document is noticed. By all means attach whole or part SOPs to the walls where it is of use, but ensure that they are logged as part of the controlled distribution system, so that they are kept current.

## 27.8 TRAINING

Training is a vital part of GMP, and this includes training in the relevant SOPs. It is therefore necessary to make SOPs available, for training purposes, a few days before the effective date so that staff can use the new document immediately after it becomes effective. The extent of training depends on the complexity of the task described, and on the experience level of the staff. A full training course, with proficiency test at the end, might be appropriate for certain SOPs, while for others, it might be necessary only to read them before they are effective, and a complete range of intermediate situations is possible. Part of the process of preparing and approving a new SOP might be deciding how much training is required; alternatively this can be left to the departmental supervisors, who probably best understand the capabilities and knowledge of their staff. However this is decided, it should be recorded for each SOP. Then, after the training, the trainer (if necessary) should sign a training record to indicate that she or he has given the training, and that the person trained is judged competent to carry out the task. The trainees must then sign to indicate that they have received and understood the training, and that they feel that they are competent to carry out the specified task. It is common practice, and not unjustified, to argue that the author of an SOP is automatically considered trained in the task described, and is also qualified to train others. Where an organisation takes this view, this policy must be included in the SOP(s) that cover training in the use of SOPs. The task described in the SOP cannot be carried out by staff who have not been appropriately trained, and for existing staff who are to carry out the task, the period before the SOPs effective date is required. It is very important to ensure that new staff, or staff who

missed the initial training for some reason, do not carry out the task until they too have received the appropriate training.

## 27.9 SOP PERIODIC REVIEW AND CHANGE

As with other GXP's the GMP's require that SOP's are up-to-date, and that there is a review of each SOP after it has been in operation for a time. The interval for such periodic reviews is not prescribed, and different organisations have different standards. The two key factors to bear in mind in setting the interval is that it must not be so infrequent that SOP's become out-of-date, and it must not be so frequent that the work involved in reviewing SOP's is excessive (or, worse still, the review period is not complied with). Intervals of 1, 2 or 3 years are common, with perhaps a majority favouring review every two years.

Of course, it is not necessary, or appropriate, to wait for the periodic review to come round to correct an error in an SOP; this should be done as soon as it is noticed. The process of amendment is, in essence, very similar to that involved in first creating the SOP. A revised version needs to be created, reviewed by the users, then formally approved, and once approved, it needs to be issued. Once the effective date of the revised SOP has been reached, the old version needs to be removed from the system, and the new version comes into use. It is important that the original signed version of the superseded SOP is kept in an archive, so that it is possible at any time in the future to look at the SOP that was in use at a particular time. The copies, if paper copies are distributed, should be destroyed. This can be achieved either by requiring the copies to be returned to the appropriate group for destruction, or by requiring that the user, or by requiring the person responsible for the SOP file to destroy the superseded version. In this case, the responsible person should return a record of the destruction to the documentation group.

Sometimes, an SOP error is so egregious that it must be corrected immediately, without waiting for a revised issue to be prepared, approved and issued. Under these circumstances, it might be appropriate for the documentation to make a hand-written, signed and dated, amendment to every copy of the SOP. This amendment should be checked by an appropriate person. If such amendments occur, then they should be followed immediately by a revision of the SOP, so that the version with the hand amendment is in use for the minimum period.

However, for many SOP's, particularly after an initial amendment has corrected obvious errors, there are few calls for revision because the user spots an error. This is when the periodic review process comes into play. The purpose of the review is to answer several questions: Is this SOP still required? Does this SOP describe what we want done? Could it describe the required task better? Lastly, does it describe the best way to carry out the task? The periodic review should be a formally documented review, by the staff responsible for use of the SOP. If no change is necessary, then either a record can be kept of the review and the SOP remains unchanged, or it can be re-issued, with a new version number and effective date. The latter is more work, and means changing pieces of paper with no change in text, but it does make it clear to all that the SOP has been reviewed and is still up-to-date. In this case, the History section of the SOP would simply show "Periodic review; reissued without change" and the date.

## 27.10 DEVIATIONS FROM SOPs

These will happen, either by deliberate non-compliance (as may occur in drug development, for example), because a piece of equipment does not operate as described in the SOP, or it may not be available, or finally as the result of a simple oversight or error by the operator. The full workings of a deviation system are not the subject of this chapter, but the key points are that all deviations



must be recorded, investigated, and acted upon. It goes without saying that the operation of the deviation system must be described in an SOP.

## 27.11 WHAT SOPs ARE REQUIRED?

All activities that have any impact on the potency, purity, identity or quality of the product must be described in SOPs. This means that, as relevant, there should be SOPs covering the activities listed below. Depending on the exact nature of the activity in a particular organisation, it may be that an item in the list requires more than one SOP, or that SOPs covering other topics are needed; however, the listing describes the major areas where SOPs are needed. This listing is structured around the main headings in the EU GMP, but the exact location of each SOP topic in this listing is not critical.

### 27.11.1 Quality Management

*Organisation charts, preparation and revision:* An organogram is required for the organisation, this SOP sets out who is responsible for their preparation, review and approval, and distribution.

*Responsibilities:* Linked to the organisation's structure as defined in the organograms, there need to be SOPs defining the responsibilities of the particular groups, most particularly the QA function.

*Investigation of deviations:* As mentioned above, it is inevitable that, despite the most carefully written SOPs, and the most thoroughly trained staff, deviations will occur. There must be an SOP detailing how deviations are recorded and investigated, and how corrective and preventative actions are approved and their implementation monitored, as well as the allocation of deviations to root causes and the trending of root cause data (see Chapter 3).

*Change control:* Changes in facilities, equipment, procedures and materials are certain to be required. There must be a system for requesting, reviewing and approving (or rejecting) changes, for assessing their likely impact on the current qualification or validation status of the subject of the change, and for monitoring the implementation of the change and any re-qualification or re-validation work. The systems and documents required by the change control mechanism must be described in one or more SOPs.

*Batch numbering:* So that products can be traced from manufacturing (see Chapter 29) through to their use or destruction, there must be a system to uniquely identify each batch of material, that is a batch numbering scheme. This needs to be described in an SOP that covers the definition of a batch, the format and allocation of batch numbers, and how these are logged.

*Batch release procedure:* Even during drug development, drug products require formal release (see Chapter 30) before they can be administered to human subjects. After May 1 2004, this release will have to be carried out by a qualified person (QP). There needs to be an SOP (or more than one) that describe what documents and other information will be made available to the QP, what checks the QP will carry out, or have carried out on his or her behalf, and how the QP will signify release of a batch.

*Validation master plan (VMP) preparation and approval:* The VMP is a living document, setting out the organisation's policies on validation, allocating responsibilities, specifying what is to be qualified and validated, and to what extent, and often also serving to list the actual validation or qualification status of each item or procedure listed. The process by which the VMP is created, reviewed, approved, distributed and kept up-to-date must be set out in an SOP. During drug development, the extent to which processes are validated will change as development proceeds. An SOP is required, therefore, to specify the organisation's policy on the extent of validation at different stages of development, and how this is monitored. An outline of the topics that should be included in the Validation Master Plan is given in Annex 15 to the EU Guide to GMP,



“Qualification and Validation”, and in the PIC/S publication “Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation”, (PI 006–2).

*Supplier selection and evaluation:* There needs to be a policy on how suppliers are selected and evaluated, and whether initial or periodic audits are undertaken.

*Dealing with regulatory inspections and customer audits:* After 1 May 2004, inspections of development manufacturing facilities by national regulatory authorities will become routine throughout the European Union. While it is not essential to have a document describing how these are handled, who is responsible, *etc.* it certainly will make for a smoother inspection if everyone who is involved knows what is expected of them. Similarly, contract manufacturers and analytical facilities are subject to many audits by clients, again a well-thought-out process for dealing with these makes the audit go more smoothly, which benefits both the client and the contractor. These documents are also the place to put statements of company policy such as whether auditors are allowed to use cameras or video equipment on site. Such statements will not, at the absolute end, deter a government inspector who is collecting evidence, but if matters get to that stage, no SOP will protect you.

### 27.11.2 Personnel

*Training of new personnel:* This document describes the induction and general GMP training given to every new employee, and how their task-specific training is decided. There should also be written descriptions of how all training is documented. Finally, the requirement for periodic refresher training in relevant parts of GMP ought to be specified.

*Job descriptions and curricula vitae (CV):* A job description, so that staff are clear on what they are expected to do, and a CV, so that the prior experience of each staff member is clear, are important documents to show, together with the training record, that each member of staff has the experience, education and training (or any combination of these) to carry out his or her specified duties. The system should be specified in an SOP.

*Curricula vitae for consultants:* Consultants can be used for the whole range of GMP activities, if an organisation so wishes. However, like regular staff, it is important to be able to show they were appropriate for the job they carried out, so an SOP should specify that a detailed CV will be obtained from each consultant, preferably before they carry out the work, and should specify who is responsible for storing these.

*Factory clothing and personal safety equipment:* There need to be one or more SOPs detailing the appropriate clothing to be worn in particular manufacturing or laboratory areas, and, if appropriate, how this is to be put on and removed. Similarly, if personal safety equipment (*e.g.* safety glasses, face shields, gloves, *etc.*) are required in certain areas, or for certain processes, this should be set out in the appropriate SOP.

### 27.11.3 Premises and Equipment

*Cleaning of facilities:* There need to be SOPs describing how the various areas of the facility are cleaned, at what frequency, using what cleaning agents and processes, and how appropriate cleanliness is monitored. For less critical areas this might be simple visual inspection by the area supervisor, whilst for the most critical area there might be a sophisticated environmental monitoring programme. All of this needs to be described in SOPs, which should also describe how cleaning is recorded, and what happens if the cleanliness monitoring shows an area to be insufficiently clean.

*Operation of all items of equipment (including cleaning):* For each item of equipment used in the manufacture or testing of products, there need to be one or more SOPs detailing how the equipment is to be used, and how it is to be cleaned. This may also include how cleanliness is evaluated before the next use. This should include specification as to how equipment is to be labelled to indicate its status (e.g. “Clean”, “awaiting cleaning”, “in use”, etc.). The routine maintenance and calibration programmes for the item also need to be specified in writing.

*Routine monitoring of temperatures, humidity, etc. in controlled areas:* In any manufacturing or testing area where the temperature, humidity or other environmental parameter is critical, there must be a system to monitor that parameter. This might be as simple as routine temperature monitoring of a warehouse, with fairly wide limits, or it could be the sophisticated monitoring programme for an aseptic filling room, where temperature, humidity, relative air pressurisation, and non-viable airborne particulate matter all need to be monitored and controlled with tight limits. In addition, the SOPs on such monitoring should describe what actions are to be taken, by whom, in case the monitored parameters go out of the specified limits.

*Maintenance of utilities and equipment:* As appropriate, these can either be included in the SOPs for operating the item or service, or separate SOPs can be set up. The choice should be made on the basis of convenience for the users of the documents.

*Calibration:* Without calibration, measurements are of very little value. There must, therefore, be SOPs setting out the calibration programme for all critical measuring equipment, including how the frequency of calibration is established, setting out the tolerances on calibration, and finally detailing what is done, by calibration engineers, equipment users and QA, when a calibration exercise finds that an instrument is out of its tolerance limits.

*Equipment and facility qualification and re-qualification:* There need to be policies on qualification (see Chapter 34), to describe the responsibilities of the staff involved, how protocols and reports are written and approved, and what is done when a validation exercise does not meet the acceptance criteria. Re-qualification may be appropriate after major maintenance, after significant change, after unexplained failure, and for certain critical equipment, periodic re-qualification may be appropriate. The SOP needs to describe how the decision on re-qualification is made, and how the set of tests that consider re-qualification are decided. If not set in the Validation Master Plan, this SOP also ought to set recalibration periods for critical equipment.

#### 27.11.4 Documentation

*The SOP system:* This is the first SOP needed, describing, SOP format, preparation and approval, distribution, amendment and periodic review and SOP training.

*Other documents:* There are several other types of documents needed, such as specifications, master formulae, process instructions, batch manufacturing records and other general records. The systems by which these are prepared, approved, issued and amended need to be specified in one or more SOPs. Obviously, these systems will be easier to run if they share as much as possible with the SOP system.

*Completion of records:* There need to be one or more SOPs that set out how records are to be written (in permanent ink, of course), how corrections are made to erroneous entries in records, and how numbers are rounded. If the organisation is large, or if the policy is to use initials in place of full signatures, then there also needs to be a signature log, like everything else, which needs to be described in an SOP.

*Record retention:* The requirements for retention of records which are set in the GMPs, but there should be an SOP setting out the organisation's minimum retention periods, and how the decision whether to destroy a document when its retention period is up is made.

### 27.11.5 Production

*Receipt of raw materials:* How raw materials are received, inspected and where they are stored, both when in quarantine and after release for use (see Chapter 28).

*Manufacturing processes:* Much of the detail in a manufacturing process can appropriately be included in the batch manufacturing record (see Chapter 29), which becomes both an instructional document as well as the raw data concerning manufacturing. Additionally, there should be SOPs detailing how to operate the process equipment. However, it could be that certain manufacturing activities could be usefully described in SOPs.

*In-process sampling and testing:* Detailed sampling instructions can be included in batch manufacturing records, but it may be appropriate to have these activities set out in SOPs instead.

*Packing and labelling processes:* Just as for manufacturing processes, these may be described in batch packing and labelling records (see Chapter 28), or in SOPs, as is convenient for the organisation. One topic that is perhaps better dealt within an SOP is the matter of reconciliation of product and packaging materials, including the acceptable range for reconciliations and the actions taken if these limits are exceeded.

*Label printing, etc:* If labels are printed in-house, then detailed SOPs are required covering how the text is generated and how the labels are printed. Whatever the source of the labels, SOPs are needed to cover how labels approved by QA or quality control (QC) are stored and issued, how label reconciliations are performed, the tolerance on reconciliation and what is done when these tolerances are breached, and how additional labels can be prepared and how excess labels are destroyed.

*Material labelling:* As materials move around the facility, there needs to be clarity on their identity and status. There must therefore be SOPs describing how materials are to be labelled, both as to identity and status.

### 27.11.6 Quality Control

*Receipt and labelling of samples:* An analytical result is of no value if the sample is not representative (dealt with in sampling SOPs), and if it is not certain what it represents, and if the sample has been stored under incorrect conditions. There must, therefore, be an SOP describing how samples are logged into the analytical laboratory, how they are labelled, how they are to be stored, and how they are issued to analysts for study.

*Analytical methods:* These are often considered as a separate class of documents to SOPs. However, whatever they are called, they still need to be reviewed, approved, issued, and in general, controlled in a similar way to SOPs.

*Out-of-specification results handling:* A critical SOP, this should spell out in detail the steps taken when an out-of-specification result is obtained.

*Preparation of certificates of analysis:* The certificate of analysis is both a summary of the analytical data, and, in some situations, the document that shows that a batch of product has been released for use or distribution.

*Label inspection:* This SOP or SOPs should cover how label text is verified prior to printing, how printed labels are sampled and inspected, and how any variable information overprinted on labels (most typically batch number and expiration date) is verified.

*Sampling (including retention samples where appropriate):* Without samples that are representative of the batch of material sampled, analytical work is of little value. There, therefore, need to be SOPs describing how samples are taken from raw materials, intermediates and finished products, what sample containers are used, how these are to be labelled and stored before analysis. The sampling tools, and how these are cleaned, also must be described. Additionally, there is a requirement that

samples of starting materials and finished products are retained, so there needs to be an SOP on how these are taken, labelled and stored.

*Labelling of raw materials:* It is important that raw materials are traceable, that is it is possible to unequivocally identify the batches of raw material that were used in a batch of finished product; furthermore it is an important part of GMP compliance that raw materials that have not been approved by QA or QC are not inadvertently used in manufacture (see Chapter 28). The mechanism by which traceability and status are controlled can be via labelling alone, or it might be achieved by a computerised inventory management system that only allows allocation of released batches for manufacturing. However it is achieved, there will be a requirement for labelling of raw materials on receipt, and possibly when released for use. All of this needs to be specified in SOPs.

*Examination of retention samples:* It is a requirement of US GMP that retention samples are examined visually every so often. Although it is not a specified EU GMP requirement, it might be appropriate to adopt this as it requires little effort, and can reassure that major problems have not arisen. If it is to be done, then of course the process needs to be described in an SOP.

*Stability testing:* For a product in development, stability studies following ICH guidelines are necessary to establish a shelf-life (see Chapter 29). Once a product has been approved for marketing, regular stability testing, perhaps on one batch per year, is necessary to demonstrate that the shelf-life claim is actually met in real production conditions. Lastly, if a process, equipment or material change might have an impact on product stability, again a stability programme is required. Therefore, there must be an SOP describing how stability studies are designed, executed and reported.

### 27.11.7 Contract Manufacture and Analysis

*Selection of contractors:* This SOP covers how the GMP aspects of contractor selection are carried out, for example technical and GMP compliance evaluation. It does not deal with financial or business aspects of the relationship, as these are irrelevant to GMP compliance, and should not be described in SOPs.

*Technical agreements:* Where a manufacturing process or step, or an analytical method, is carried out by a contractor, it is an essential requirement of EU GMP that there is an agreed written contract between the contract giver and the contract acceptor, setting out what is expected of both parties, and where the responsibilities lie. This can be part of a commercial contract or separate, and is called by a range of names, including Quality Service Agreement. Whatever it is called, the system by which these agreements are prepared and the system of review and approval, must be covered by an SOP.

*Audit of contractors:* It is usually appropriate to carry out periodic audits of contractors. The policy on such contractor audits, including the frequency, should be set out in an SOP.

### 27.11.8 Complaints and Product Recall

*Receipt and investigation of complaints:* Although product–quality related complaints against IMPs are rare, it is important to have a procedure setting out how any complaints will be investigated and reported on. In addition, it may be valuable to include a periodic review of Adverse Event reports to determine if these indicate a problem with any particular batch of IMP.

*Product recall:* This is a vitally important SOP, and one that is difficult to get right, as fortunately recalls are a rare event in drug development. A useful analogy might be the air bag fitted in many

cars. You hope that it will never be needed; but in event of an emergency, it is vital that it works first time. So it is with the recall procedure. Therefore, it may be worthwhile including a provision for periodic “mock” recalls, where the systems are tested without actually recalling the product.

#### **27.11.9 Self-Inspection**

*Internal audit procedure:* This SOP sets out what is covered by the internal audit programme, who carries out the audits, at what frequency, how the audits are reported, and how any negative observations are dealt with (see Chapter 31). One important point is that reports, or summaries of the most significant findings, must be given to senior management, both so that they understand the situation within their own organisation, and so that appropriate resources can be devoted to dealing with problems.

#### **27.12 CONCLUSION**

Although SOPs are not the sole requirement for achieving well-controlled and efficient manufacturing and testing of pharmaceuticals, and are not the sole criterion of GMP compliance, there can be no doubt that a well-designed SOP system is a major tool in achieving both goals.



## CHAPTER 28

# Release of Bulk and Filled Finished Product

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Well within living memory, in the majority of pharmaceutical manufacturers, a standard operating procedure (SOP) defining criteria for batch release, if there had been one, would simply have read: “Compare the test results on the submitted sample with the specification for the product. If these results comply with the spec., release the batch”. Very often the person(s) making the release decision would have had little or no knowledge of how representative the sample was, it having been taken by the production department, in accordance with no specific sampling plan or scheme.

Thirty or forty years on, although it is now common for samples to be taken by quality control (QC)/quality assurance (QA), rather than by production personnel, the question of the scheme or plan for taking a truly representative sample remains largely unresolved. The EC GMP Guide,<sup>1</sup> for example, states:

### *Sampling*

*4.23 There should be written procedures for sampling – describes the methods and equipment to be used ... the amounts to be taken ...*

- and the US “cGMPs”<sup>2</sup> (in Subpart F– Sec. 211.110, Sampling and testing of which includes materials and drug products) demand that:

*(b) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.*

- And also (in Subpart I--Laboratory Controls) that:

*(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labelling, and drug products conform to appropriate standards of identity, strength, quality, and purity ... Samples shall be representative and adequately identified.*

However, neither of these two regulatory pronouncements offers any advice or direction on what constitutes an acceptable sampling method or amount, on what is an “appropriate” or “representative” sample or on what is a “scientifically sound” sampling plan. (For a more detailed analysis of the problem of taking meaningful samples, in the context of national and international guidelines on the subject, see Sharp.<sup>3</sup>)



The problem, of course, lies in the dubious validity, in this context, of statistical sampling plans, which of necessity are based on a prior acceptance of a predetermined level of defective items in a batch. It has been stated, in reference to the frequently cited US “Military Standard Tables” that:

*“... we know that they are made for other purposes, where a certain degree of error is easier to accept than for pharmaceutical products.”<sup>4</sup>*

and that

*“... the consumer of drugs wants a “zero defect” quality, which is incompatible with the very theory of control based on sample inspection.”<sup>5</sup>*

(In passing we may note that, while from a philosophical standpoint “zero-defect” quality may be impossible to achieve, it is what the consumer of pharmaceutical products, not unreasonably, wants and expects.)

Well-stirred bulk liquid products in the form of readily soluble materials dissolved in a solvent vehicle may be considered to be homogeneous, given that the manufacturing process has been adequately validated to that end, and that the validated process has been followed (see Chapter 29). Thus any sample of the bulk liquid may reasonably be taken to be representative. However, if a bulk liquid product is sampled and tested before filling into a number of discrete containers (*e.g.* as a guard against the cost of filling and labelling a product which is later rejected for inhomogeneity), it is an obvious good practice to take samples for assay from the filling line, at the beginning, the middle and the end of the filling run.

Sampling of liquid suspensions, emulsions and the like may present greater problems. Process validation should have established that, at the completion of the bulk batch the active ingredient(s) is/are uniformly and homogeneously distributed. However, against the possibility of separation during holding and transfer to filling, sampling from the filling line (beginning/middle/end) must surely be obligatory. Similar considerations also apply to the sampling of creams and ointments.

With regard to unit dose solids (tablets, capsules and the like) the commonly employed in-process controls on tablet weights and thickness, and on capsule-fill weights, will contribute towards the assurance of the uniformity of these products. For an impressive analysis of the problems of sampling bulk powder mixtures, with comprehensive guidance on sampling filled capsules and compressed tablets, see PDA Technical Report No. 25.<sup>6</sup> An original impetus for this report was the so-called “Wolin Decision” (*i.e.* the judgement of judge Wolin in the US *vs.* Barr Laboratories case) which *inter alia* laid down procedures and methods for sampling bulk powder mixtures (see Chapter 29). The report clearly shows that, despite the great store that the US FDA placed upon this judgement as a banner to wave and a cudgel to bludgeon the industry, the learned judge’s views on sampling were fundamentally flawed, in both practical and statistical terms.

While one would not wish to suggest that end-product sampling and testing should or could be abandoned entirely (see section on “Parametric Release” in Chapter 31 “GMP for Sterile Products”), it is the increasing and deepening realisation of the severe limitations of sampling and testing as a measure of product quality which has led to the realisation that product release must be based on the careful and critical evaluation of a whole range of other factors.

Certainly, opinions and practices regarding matters to be considered in making a decision to release or not to release, have changed markedly for the better over the years. This has been the result of regulatory pressure and the growing realisation that “complies with spec.”, by itself, is a very poor determinant of product quality.

European and US regulatory edicts may be taken as exemplars of this salutary shift in emphasis:

The US Code of Federal Regulations (CFR)<sup>2</sup> Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart J – Records and Reports, Sec. 211.192 Production record review reads:

*All drug product production and control records, including those for packaging and labelling, shall be reviewed and approved by the QC unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.*

The EC Guide to GMP<sup>1</sup> states:

“1.4 QC is that part of GMP which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory.

The basic requirements of QC are that:

(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk and finished products is formally assessed against specification. *Product assessment includes a review and evaluation of relevant production documentation* (author’s emphasis) and an assessment of deviations from specified procedures.

And

4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the Qualified Person(s) ...

And

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.”

The question of what exactly are the factors to be taken into account before the decision is taken to release a batch of product for sale or supply was given a sharper, more detailed, focus in the joint (Royal Pharmaceutical Society, Institute of Biology and Royal Society of Chemistry) “Code of Practice for Qualified Persons”. This has been reprinted in the Medicines Control Agency’s (MCA’s)

“Rules and Guidance for Pharmaceutical Manufacturers, 2002”,<sup>1</sup> and therefore may reasonably be considered to have been granted a regulatory *imprimatur*. This code states *inter alia* that:

“Before certifying a batch prior to release the Qualified Person (QP) doing so should always ensure that the following requirements have been met:

5.1 Marketing authorisation (MA) and the Manufacturing authorisation (MA) requirements for the medicinal product have been met for the batch concerned.

5.2 The principles and guidelines of good manufacturing practice as laid down in Directive 91/356/EEC (Human) or Directive 91/412/EEC (Veterinary) and as interpreted in the “EC Guide to GMP” have been followed.

5.3 The principle manufacturing and testing processes have been validated.

5.4 All the necessary checks and tests have been performed and account taken of the manufacturing and packaging conditions including a review of batch records.

5.5 Any changes or deviations have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to and approval by the MCA, or VMD.

5.6 Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover changes or deviations.

5.7 All necessary production and QC documentation has been completed and endorsed by suitably authorised staff.

5.8 Regular audits, self-inspections and spot checks are being carried out by experienced staff.

5.9 All relevant factors have been considered including any not specifically associated with the output batch directly under review (*e.g.* calibration and maintenance records, environmental monitoring).

5.10 The legal requirements regarding imported products have been fully met.”

This passage could be considered as summarising a number of significant elements of QA/GMP. It also poses a formal antithesis to the old, discredited view that the quality (and hence “release-worthiness”) of a batch of product can be evaluated on the basis of end-product test results alone.

In July 2001, the European Commission published a new annex (no. 16) to the EU Guide to good manufacturing practice (GMP), on “Certification by a Qualified Person and Batch Release”.<sup>7</sup> It concerns “in particular those cases where a batch has had different stages of production or testing conducted at different locations or by manufacturers and where an intermediate or bulk production batch is divided into more than one finished product batch”. It does, however, include a statement of the routine duties of a qualified person (QP), thus:

## **8. Routine duties of a Qualified Person**

8.1 Before certifying a batch prior to release the QP doing so should ensure, with reference to the guidance above, that at least the following requirements have been met:

- (i) the batch and its manufacture comply with the provisions of the marketing authorisation (including the authorisation required for importation where relevant);
- (ii) manufacture has been carried out in accordance with Good Manufacturing Practice or, in the case of a batch imported from a third country, in accordance with good manufacturing practice standards at least equivalent to EC GMP;
- (iii) the principal manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;

- (iv) any deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorisation have been notified to and authorised by the relevant authority,
- (v) all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;
- (vi) all necessary, production and quality control documentation has been completed and endorsed by the staff authorised to do so;
- (vii) all audits have carried out as required by the quality assurance system;
- (viii) the QP should in addition take into account any other factors of which he is aware, which are relevant to the quality of the batch.

Even the most cursory examination will suggest that this list of “Routine Duties ...” is based upon, and largely follows, the original publication of the three joint UK professional bodies, as indeed it is and does. As ever with these European statements that have been lifted from documents originally written in a language recognisable as decent English, the transference has been made without any notable enhancement of clarity of expression or linguistic felicity.

#### **“Release by Qualified Person”**

The requirement for a manufacturer of medicinal products to have the services of at least one “Qualified Person” was originally established in the European law, in Directive 75/319/EEC<sup>8</sup> (since consolidated in the newer codified Directive 2001/83/EC (Human Medicines) and 2001/82/EC (Veterinary Medicines)). For readers unfamiliar with this concept, it needs to be noted that in this context the term “Qualified Person” has a specialised, defined, meaning: it does not simply mean a person who is qualified.

Every company manufacturing pharmaceuticals in the EU, and/or importing pharmaceuticals from outside the Community must have at least one “Qualified Person”. The functions of the QP are simply stated in Directive 75/319/EEC. In the case of MANUFACTURE, the QP is legally required to

*“Secure that each batch of product has been manufactured and checked in compliance with the law in the member state, ... and in accordance with the Marketing Authorisation.”*

and he/she must certify to that effect “... in a register or equivalent document”. In this context, an appropriately signed Batch Manufacturing Record (for example) is considered to be an “equivalent document”.

The concept derives from the traditional arrangements in some European countries, notably France and Belgium, where it is a legal requirement for a manufacturer to appoint a “Responsible Pharmacist” (or *Pharmacien Responsable*), who could be in charge of both Production and QC. In the Directive, the Responsible Pharmacist was converted to the “Qualified Person”, presumably because this, more generalised term, would be more acceptable to and would more readily find accommodation with traditional practices in the majority of member states. A British Manufacturer’s License, for example, has to name, as it always has since the implementation of the UK Medicines Act (1968), a Production Manager and a QC Manager. In addition, under the European Directive, one or more QPs have also to be named, who may or may not be same person(s) as the QC Manager or the Production Manager. (Strangely, despite the sound and commonly held view that, as the EC GMP Guide<sup>1</sup> puts it, in para. 2.3 “The heads of production and QC must be independent from each other”, there is a very strong implication in that same paragraph that “The Head of Production” may also function as a QP.)

Under “Grandfather” transitional provisions (now virtually expired) it was relatively easy for anyone already in post to be accepted as a QP. Under the Permanent Provisions, the requirements

of the Directive in terms of education, professional/academic qualifications, knowledge and experience are somewhat more rigorous. They include:

“FORMAL QUALIFICATION ... after recognised course of Study, ... bearing at least upon ...  
Applied physics  
General and inorganic chemistry  
Organic chemistry  
Analytical chemistry  
Pharmaceutical chemistry, including analysis of medicinal products  
General and applied biochemistry (medical)  
Physiology  
Microbiology  
Pharmacology  
Pharmaceutical technology  
Toxicology  
Pharmacognosy (medical aspects).”

In addition, there is a requirement for “PRACTICAL EXPERIENCE” of 2 years ... or 1 year ... or 6 months, depending on the nature of the “formal qualification”.

In Britain, the approach to implementing these requirements has tended to differ from that of probably all the other member states, where the attitude has been a somewhat *laissez-faire* one of “What’s new? We’ve always done it this way”. The British Health Ministers delegated to the relevant professional bodies (The Royal Society of Chemistry, The Royal Pharmaceutical Society and The Institute of Biology) the responsibility for maintaining and publishing registers (now, in fact, a single joint register) of those considered, in terms of all the criteria, acceptable as QPs. While the MCA (now the MHRA) has the last say on the acceptability of an applicant to be named on a License, it is not normal for them to reject a person who is listed in the joint professional register.

The three professional bodies have produced a joint statement on knowledge and experience requirements, as well as the Code of Practice for QPs, which has already been mentioned. Colleges and the like run three-year post-graduate courses for aspirant QPs. It seems unlikely that same intensity of purpose applies across the community.

It is believed that the intention is that there should be reciprocity of QP status across the community, but that has yet to be tested, and it could be that some member states will not be inclined to accept that any person other than a pharmacist could be a QP.

One other function of the QP is still to be mentioned: In the case of the importation of pharmaceutical products, into EC from a non-EC source, the QP must also ensure that each imported batch undergoes a complete re-analysis in the importing state, even if certificates of analysis of confirmed reliability are available, and he must certify in writing to that effect. (In some specific cases a waiver may be permitted.) No such requirement for re-analysis applies to export/import between EU member states.

The expression “Release by QP” is commonly heard, or read, in relation to release for sale or supply of bulk or finished pharmaceuticals. This is, perhaps, not entirely surprising, since there are at least two references (e.g. paras 4.24 and 7.4) in the EC GMP Guide<sup>1</sup> to “release of a product by a QP”. Paragraph 4.24 for example reads:

4.24 Written release and rejection procedures should be available for materials and products, and *in particular for the release for sale of the finished product by the Qualified Person(s) (QP) in accordance with the requirements of Article 22 of Directive 75/319/EEC.* (Author’s emphasis)

The belief that the QP is responsible, and indeed potentially liable, for the release of finished product has caused concern among a number of practising QPs, fearful of the legal consequences should a batch of product which they had “released” cause harm. Very recently, however, the position has been clarified by the UK MCA who have confirmed that “QP certification comes before, and is distinct from, the decision to release a batch to the market”,<sup>9</sup> and that:

Medicines legislation requires certification of a batch of a licensed relevant medicinal product by a Qualified Person (QP) prior to release. The legislation is silent on who should take the decision to release a batch following QP certification and who takes the responsibility for that decision. The release of a batch to the market is a commercial decision; therefore, the identity and responsibilities of the “releasing officer” are matters for the company concerned.<sup>10</sup>

It would appear, therefore, that in strictly legalistic terms, in Britain at least, there is some doubt about who takes the ultimate responsibility for the release of a batch of bulk or finished pharmaceutical product. However, few would doubt that the rational, professional, and ethical criteria for the “releasability” of a batch of pharmaceutical product are those as set-out in the “Code of Practice for Qualified Persons” and/or the “EC Guide Annex 16”, and as encapsulated in The US Code of Federal Regulations (CFR) Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart J – Records and Reports, Sec. 211.192 (*vide supra*).

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# Good Manufacturing Practice for Investigational Medicinal Products

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## 29.1 INTRODUCTION

The requirements and expectations for good manufacturing practice (GMP) compliance in the manufacture of investigational medicinal products (IMPs) within the European Union (EU) changed dramatically in 2004, with the implementation of the Clinical Trials Directive. Although the original European Commission Directive that lay at the heart of the GMP requirements in Europe (91/356/EC) limited its scope to those medicinal products that require a marketing authorisation, there have been EU guidelines on the manufacture of IMPs (Annex 13) for several years. This is in marked contrast to the situation in the United States, where the FDA requires that materials intended for use in a clinical trial are manufactured in accordance with the principles of GMP as set out in 21 CFR 211. There has been recognition, in practice, that full compliance with all the requirements is not practical, especially early in the development programme, but no formal guidelines for investigational product GMP has been published.

In the UK, this lack of any European legal basis for application of the requirements of 91/356/EC to materials without a marketing authorisation used in clinical trials resulted in a situation where the regulatory authorities expected that materials for clinical trial use were made in compliance with the principles of GMP, but they had no way of verifying that this was the case, or of taking action where it was not. In the UK, there was for some years a system of voluntary inspection, but this, of course, only dealt with organisations that were willing to volunteer.

The situation in other European countries was rather varied; some had quite tight regulation and inspection of clinical trial manufacturing operations, while others had more lax supervision. With the coming into force of the Clinical Trials Directive (2001/20/EC), both the GMP directive (91/356/EC, now renumbered as 2003/94/EC) and the Annex 13 guideline have been revised, GMP compliance became a legally enforceable requirement for the manufacture of IMPs. All IMP manufacturing sites will be inspected and licensed if found to be appropriately GMP compliant. At the time of writing (Summer 2004), some countries had still not fully implemented the directive, but this was expected shortly.

The GMP for IMPs should then be relatively simple and no different from the expectations for a licensed product, were it not for the nature of pharmaceutical development. The nature of

pharmaceutical development precludes the application of normal GMP controls for a number of good reasons:

- Particularly during the early stages of development, relatively little is known about the active pharmaceutical ingredient (drug substance). If it is a chemical entity, it is usually manufactured on a relatively small scale, with frequent changes in the synthetic route. Similarly, biotech products will be made initially on a small scale, using a process that has not been optimised, or even fully developed. Irrespective of its mode of production, the methods used to analyse the active pharmaceutical ingredient will be at a relatively early stage of their development. In many cases they will be restricted to the assay of the active pharmaceutical ingredient itself, with little-established ability to resolve either degradation products or impurities. To a great extent, this is all recognised by the GMP for active pharmaceutical ingredients (APIs, also commonly known as drug substances), ICH Q7A (incorporated into the EU Guide to GMP as Annex 18), in its section 19, “APIs for use in Clinical Trials”.
- Information about active pharmaceutical ingredient properties will be limited. If development is well planned and executed, active pharmaceutical ingredients will have been made available for characterisation, stability and analytical development work, and a basic package of information to assist in the proper selection of the early dosage form will be available. All too often, however, a mixture of ignorance and cost cutting means that the information required is not available. This makes pharmaceutical development less soundly based.
- The drug product will also be at a very early stage of development; often a simple solution or a hand-filled capsule is all that can be produced as a result of limited drug supply.
- The analytical method for the drug product will normally be based on the method used for the active pharmaceutical ingredient itself, rather than be developed to meet the particular requirements of the dosage forms used in clinical trials. As a result, it is less reliable.
- Even Phase 1 trials, the very first administration of the drug to humans, may be carried out in a placebo-controlled double-blind study. In making materials for blinded trials, the manufacturer breaches one of the cardinal principles of GMP by producing two different products (active and placebo) that look as identical to one another as can be achieved. This completely reverses one of the most important and fundamental requirements of GMP, which is to be able to identify the product throughout its manufacturing life.

Individually, these differences create substantial problems for the quality management process. The combined effect of these is that, although the general requirements of GMP certainly apply to IMPs, GMP has to be re-interpreted and re-applied in the context of IMPs. The differences result in a unique set of responsibilities of the person releasing active pharmaceutical ingredient for the manufacture of IMPs as well as the IMPs themselves.

## **29.2 GMP FOR DRUG PRODUCT MANUFACTURE**

This section of the chapter will concentrate on the differences between the requirements of full GMP and the requirements for IMPs as set out in Annex 13.

### **29.2.1 Quality Management**

There can be no dispute that an IMP manufacturing operation needs a strong quality management system. Indeed, given the need for flexibility to deal with constant change, while retaining a full GMP “state of control” to assure continuing product quality and safety, the quality management system needs to be very strong.

There are many companies undertaking drug development that do not have the necessary manufacturing capacity and know-how, and therefore contract out this part of the work to a contract manufacturer. However, the original development organisation acts as the sponsor for the clinical trial itself.

The ICH GCP guidelines state that the study sponsor should ensure that the IMPs are manufactured in accordance with any applicable GMP. The knowledge and understanding of GMP issues of the study sponsor is often very different from that of the IMP manufacturer. The study sponsor may not have a strong quality management system. In many small organisations embarking on a drug development, quality management is at worst non-existent and at best limited. Small organisations developing one, or a few, new drugs do not have enough work in the early stages for full time quality personnel. This means that the sponsor organisation may not have the expertise, or understand the requirement, to assess GMP compliance by the contract-manufacturing organisation.

As a result, the sponsor organisation becomes entirely and yet unwittingly dependent on the quality management system of the contractor's quality management organisation.

The proper situation is that the quality management system within the study sponsor should comprehensively address the quality issues surrounding the analysis and release of active pharmaceutical ingredient and IMP alike. Where the organisation sponsoring the clinical study is not in a position to resource and execute this activity in its own right, it should use a properly qualified expert in IMP quality management to ensure that either

- a quality management system is (put) in place in the sponsor organisation, sufficient to control the manufacture and release of active pharmaceutical ingredient and IMPs

or

- the sponsor responsibilities under Annex 13 and the Clinical Trials Directive are wholly discharged by the contractor commissioned to prepare the IMP.

If the latter process is selected, it is incumbent on the expert to explain to the senior management team in the sponsor organisation, in simple and unambiguous terms, the nature of the sponsor's responsibilities, and the risks which they are taking by delegating responsibilities on, they do not fully understand themselves to a third party.

Nevertheless, delegation of the responsibility to the manufacturing contractor can only ever be part of the process. In the vast majority of IMP manufacturing activities, the active pharmaceutical ingredient will not be synthesised or analysed by the contractor manufacturing the IMP. The contractor may not, therefore, be able to release the active pharmaceutical ingredient as being suitable for human use as this requires, amongst other things:

- comparison of the analytical profile batch intended for human use with the active pharmaceutical ingredient used in toxicological testing,
- assessment of the significance of the differences between the human use and the toxicology batches and
- release (or rejection) of the active pharmaceutical ingredient as being suitable for use in humans.

In our experience, perhaps not surprisingly, this is not a responsibility that many contractors are prepared to take on. The contractor's qualified person (QP), assuming that one is nominated, will only be able to assess work carried out within the contractor organisation. In our view, the responsibility for releasing the active pharmaceutical ingredient for human use should lie within the sponsor organisation's quality management system, drawing on expert reports from suitable personnel both at the contractor and at the sponsor. The review and release process should be

documented in a standard operating procedure (SOP) within the sponsor organisation even if it is the only SOP in their quality management system.

### 29.2.2 Personnel

In the EU GMP, the chapter on personnel defines the duties of two key individuals, the Heads of Production and Quality Control (QC), and touches on the role of a third, the QP (who may be the Head of QC). In an IMP manufacturer, there may not be a person who, strictly speaking, is the Head of Production, but it is vital that the organisation examines the tasks allocated to this position and ensures that they are carried out by an identified individual or individuals. Given that there is usually less-known information about the drugs being developed and that the production and analytical processes may not be fully validated (see under “Validation”), the QC role may be larger than that normal for an established product, and the position of Head of QC is therefore more critical. The third individual mentioned, the Qualified Person, is a requirement that has been applied to licensed products for many years, but is new to IMPs. The role of the QP in dealing with IMPs is covered under “Batch Release”.

Another major topic of this chapter is training. This is no less important for IMP production, although given that processes are being changed as development proceeds, the emphasis may be slightly different from that found in regular manufacturing. The first key aspect of training that must be addressed is ensuring that the staff has an appropriate knowledge of GMP. Skilled Development scientists sometimes see GMP as a straightjacket, restricting their creativity and slowing down the pace of their advance. It must be explained to them that while GMP compliance certainly does impose certain constraints and burdens, it is an essential tool in ensuring that the processes are reproducible, that the results generated are meaningful and that the product is consistent; all things essential for successful development as well as for the safety of the subjects who will be given the IMP. Formal training in equipment operation is also necessary, of course, but perhaps more than is normal for manufacturing staff, development personnel need a good understanding of problem investigation, deviation recording and change control.

### 29.2.3 Documentation

The fact that a process or product is being developed does not reduce the need for documentation. There need to be top-level policy documents setting out the organisation’s approach to such topics as validation, cleaning and full SOPs for the operation of all facilities, equipment and systems. All steps in the manufacture and testing of IMPs need full records. This is often done by the use of pre-designed and authorised forms, such as the master-batch manufacturing record and forms used to collect analytical data. However, especially at the very beginning of development, changes are so frequent that pre-prepared forms may not be feasible. In this case, laboratory notebooks must be used to collect data. The advantage of this is flexibility, the disadvantage is that the amount of information recorded is not controlled as it is on a form. The only solution for this is to train staff in what must be recorded in their notebooks, and to require senior staff to check these notebooks frequently. The requirements for use of such notebooks should be very similar to those that apply to completion of forms, *i.e.* entries should be direct, immediate, legible and permanent, and entries should be signed and dated. Critical data should also be checked at the appropriate time, and such checks should be recorded in the laboratory notebook.

Another class of document required during development is specifications. In development, these are commonly set, and reviewed/revised, by a specification committee. This committee should include representatives of Regulatory Affairs, the group manufacturing the IMP, analytical development, QC and QA, and should be able to call on the support of a toxicologist and of people with clinical experience as needed. Specifications are necessary for raw materials, for critical

intermediates in the process and for the finished product. As has been mentioned repeatedly before, less is known about an IMP than a licensed product, and this has implications for all the specifications. First, it will not necessarily be known, early on, as to what are the critical indicators of material quality. This means that development specifications will tend to list many more test methods than will commonly be found later, and part of the development process is to review the test results periodically to determine which test methods are giving results that reflect the product quality. The other issue with specifications is of course the acceptance limits. Not all tests on a specification will, at first, have acceptance ranges; instead the results will be recorded “for information”. However, for certain tests (of identity, strength and impurity levels) and tests relevant to safety (e.g. heavy metals, endotoxin and sterility), acceptance criteria are essential from the beginning of development for use in human subjects. While in some cases, the limits are obvious (there can be no dispute that a product claimed to be sterile should pass the sterility test, even though the material is an IMP), the acceptance ranges on other test methods such as impurity levels have to be set after much more thought, and these will need to be reviewed frequently to make sure that they are not too wide. This review should take into consideration not only the results for all batches of IMP tested to date, but should also consider process changes that may have effects on the results of, or even the need for, certain tests. The key batches that will influence the specification limits are those used in clinical trials, and those used in the toxicology studies. In setting initial limits, bear in mind that it is relatively easy to tighten specification limits, but a relaxation of limits must be thoroughly justified and carefully assessed.

Although we have said that the general documentation requirements for the production and testing of IMPs are similar to those that apply to licensed products, the GMP for IMPs requires that these be organised slightly differently than might otherwise be the case. To ensure that all the relevant documentation is available to the QP to allow proper assessment of a batch, Annex 13 identifies something called the Product Specification File. This does not need to be a physical file, but should allow rapid location of current versions of the following documents:

*Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product.*

*Manufacturing methods*

*In process testing and methods*

*Approved label copy*

*Relevant clinical trial protocols and randomisation codes as appropriate*

*Relevant technical agreements with contract givers, as appropriate*

*Stability data*

*Storage and shipment conditions*

(Taken from Annex 13, Revision 1 July 2003)

The key point about the Product Specification File, which also means that it requires quite intensive maintenance, is that it is only of value if it is up-to-date.

#### **29.2.4 Facilities and Equipment**

In general, although the facilities used to manufacture IMPs are often smaller than those used for licensed products, and are usually used to manufacture multiple products, the requirements of the GMP apply just as much as for a licensed product. All facilities and equipment must be appropriate for the purposes to which they are put, and must be appropriately qualified. Critical equipment (such as autoclaves for terminal sterilisation) must be periodically requalified; this should be considered for all equipment as part of the change control review process. In addition, it may be valuable to review all the changes to an item periodically, to evaluate whether a series of

minor changes, each alone not considered sufficient to require requalification, together add up to a need for requalification.

As mentioned above, the main difference, beyond scale, between routine manufacturing and IMP production, is that multiple compounds may be handled in the same plant. This requires that significant consideration be given to minimising the risks of cross-contamination, especially where equipment is not product dedicated. This puts a major emphasis on cleaning, of both the facility and equipment, and on the assessment of cleanliness. Formal cleaning validation as would be applied under normal GMP is not normally possible for several reasons. Firstly, not all the properties of the compounds handled will be known (so for example it may not be possible to establish the minimum or maximum human doses) and not all the toxicology work may have been completed. Secondly, the range of compounds handled means that different cleaning procedures may be required for different groups of compounds. Lastly, the fact that compounds are not handled in defined sequences means that the calculation of maximum allowable carry-over, where sufficient information exists (to determine whether the cleaning that has been carried out has been sufficient), has to be done every time. Furthermore, it is very unusual for a clinical-trial material to be manufactured in exactly the same way for three batches to enable formal validation of the method to be completed.

This means that there is a tendency to rely on an arbitrary limit, such as not more than 10 ppm of the previous compound in the smallest batch of the next product, and the routine verification of cleaning on a batch-by-batch basis. Evaluation of the cleaning verification during contractor selection is an extremely important part of the selection process. The simplest way to avoid verification problems is to use dedicated or disposable equipment. So, for example, many active pharmaceutical ingredient manufacturers use new glassware for the manufacture of each batch of small-scale synthesis of GMP materials. Likewise the use of dedicated product contact change parts, mixing bowls and utensils in product manufacture saves a great deal of analytical work and resource.

### 29.2.5 Production

The main differences in production operations, beyond the scale as mentioned above, are the need for frequent process changes, the relatively high occurrence of planned (and sometimes unplanned) deviations during production and the general lack of any knowledge on acceptable yields (which once again puts emphasis on rigorous cleaning and assessment of cleanliness). Process changes are handled through a change control system, just like equipment changes. More than these latter, perhaps, they require review by, amongst others, the regulatory affairs group to determine whether the proposed change necessitates notification of, or approval by, the regulatory authorities before implementation.

It is quite likely, particularly as processes are changed during the development programme, that deviations will occur, both planned and unplanned. It is very important therefore that an organisation that manufactures IMPs has a well thought and robust system for capturing deviations (Chapter 31), and for fully assessing their potential impact. The deviation record must also be included in the package of documentation reviewed by the QP at the time of batch disposition.

The requirements for retention samples of IMPs can be difficult to administer. Firstly, there is a requirement that samples of the starting materials (the active pharmaceutical ingredient and all recipients) are kept. Then, sufficient sample to repeat all the testing, twice, must be taken from the bulk drug products. This must be retained for at least one year longer than the expiration date of the IMP, which can be an administrative challenge if, as is common in early development, the expiration date of the IMP is extended (sometimes on repeated occasions) as a result of ongoing stability studies. Lastly, Annex 13 requires that samples of each batch of product should be kept, including blinded product. This means that for open label kits, the retention sample taken of the



bulk drug product may be sufficient. However, for blinded studies, it is necessary to retain samples of packed kits. The easiest way to do this, without destroying the blinding or randomisation, is to pack the kits in blocks, and to identify one block as intended for retention.

(*Note:* At the time of writing, a proposed Annex 19 to the EU GMP, covering “Reference Samples and Retention Samples” was under consideration. The first draft of this stated that the “guidance may also be applied to investigational medicinal products, subject to any differences mentioned in Commission Directive 2003/94/EC, and any more specific guidance in Annex 13...”. The draft did not appear to require any changes in the information given above, but the final version must be checked when published.)

In all cases, retention samples are only useful if they are kept under correct conditions. It is a requirement of US GMP that a sample of the retained material is examined visually at least once each year, looking for any obvious deterioration. Although this is not a requirement of EU GMP, and certainly involves some effort, it seems to the authors that this is a simple check to be carried out that might reveal a significant stability issue.

### 29.2.6 Quality Control

Again, the full requirements of the GMP guidelines apply to the testing of IMPs, their starting materials and intermediates. Analytical methods, however, may well be less developed, and may not be validated (see “Validation”). Additionally, as mentioned in the section on specifications, under “Documentation”, the product may well be less well understood than a licensed product, and it may well need more QC testing.

One question that may arise is the need for separation between analytical development and formal QC testing. There are, of course, arguments both for keeping these as separate groups and for putting them together in a single department. If they are separate, then analytical development is not constrained by the need to follow GMP, they are merely obliged to use sound scientific practices. Method transfer from the development group to the users in QC, although time consuming, presents a good opportunity to assess the robustness of the method. Additionally, method development is not slowed by the need to test batches of product. On the contrary, if analytical development and QC are together, there is no concern about method transfer taking time, of analytical development generating methods that are not suitable for routine use, and less need to duplicate expensive analytical hardware. The advantages and disadvantages are evenly balanced between the two models.

### 29.2.7 Contract Manufacture and Analysis

As mentioned above, it is quite common for the manufacture and/or analysis of IMPs to be contracted out. When this occurs, a properly constructed technical agreement is an essential document. For a manufacturing situation, the technical agreement must specify, in addition to specific details of the process, the specifications of raw materials, intermediates and the final product, and how these specifications should be reviewed and revised. It should cover GMP standards expected, and for manufacturing in a country outside the EU, should specify that the manufacture must be to a standard at least equivalent to that set out in directive 2003/94/EC. The agreement should also specify how deviations, and changes, are dealt with, whether the client will be notified and where client approval will be needed prior to implementation. Finally, the agreement must make it clear who is responsible for release of the product for clinical trial use. For agreements for analytical work, again, the agreement should set out the GMP standard expected and should describe how the results are to be reported. It should cover out-of-specification results handling, ensuring that both parties clearly understand what constitutes an out-of-specification result, what happens when one is encountered and who is notified, when and how. This may be done by references to agreed SOPs, or may be spelt out in detail.



### 29.2.8 Product Recall

This is perhaps better known as “retrieval”, as it is the nature of most clinical trials that the sponsor knows exactly where drug is and should, in theory, be able to retrieve it relatively easily; whereas for a licensed product it can be distributed very widely, and the manufacturer alone does not have all the information necessary to ensure the product is traced to the individual patients. Irrespective of what it is called, it is essential to have a well thought-out procedure. A recall procedure is in some respects rather like a parachute, in that it is rarely used, but when it is needed, it must work. It is therefore important to test it periodically, at least as far as demonstrating that the organisation can, in an appropriately short time, account for all of a batch of IMPs and has the information and procedures necessary to notify quickly all the organisation and clinical trial sites that have received the affected product. In carrying out such mock recalls, however, great care must be taken to ensure that all staff know it is an exercise, so that there is no risk of a real recall being accidentally initiated.

### 29.2.9 Self-Inspection

This may be difficult in a small organisation, but having a disinterested look at your own organisation is a vital activity. The detailed process of such internal audits is not specified in the GMP, but it is not uncommon for a programme to require that each area of the company be looked at in turn over a one-year cycle. In general, regulatory inspectors will ask for evidence that a programme is in place and is being carried out, but will not ask to see individual audit reports, in case the writers of these reports will be constrained by fear that an inspector will use it to uncover issues in the company. Reports should therefore be clear on non-compliances and areas where compliance is weak; responses to internal audits should be required – these should describe what is to be done and when it will be done by. It is an essential part of the internal audit programme to keep top management aware of significant findings and of the progress of programmes to address them, as senior management allocate the company’s resources.

As mentioned elsewhere, many organisations working in the drug-development area are small, and may find it difficult to maintain an up-to-date knowledge of changing regulatory requirements and expectations. Under these circumstances, internal audits could usefully be complemented by evaluation by an external party. A check by a suitably qualified and experienced outsider can be most valuable in pointing out areas of weakness that the internal audit programme may have missed.

### 29.2.10 Annex 13

This annex to the EU Guide to GMP is entitled “Manufacture of Investigational Medicinal Products”, and it is sometimes erroneously thought of as the GMP for IMPs, at least within the EU. This is *not* the case; the annex describes the specific GMP requirements, *additional to or modifying* those set out in the rest of the Guide to GMP.

### 29.2.11 Validation

There is commonly a gradient of validation through the development of a drug, although different organisations tackle the need to have a validated process by the time the product is marketed in different ways. What follows is merely the opinion of the authors, and will need to be reviewed in the light of the properties of the drug and the nature of the disease being treated.

*29.2.11.1 Before First Administration to Man.* Any sterilisation process, and any other manufacturing process known to be critical to drug product safety, should be validated. On the analytical front, the sterility and endotoxin tests, and at least a test for identity and an assay of potency,

and the test for impurities should be validated to the standards set in ICH Q2A, perhaps with the exception of robustness.

**29.2.11.2 Development up to Phase III.** Any other critical steps in the manufacturing process should be examined during this time, with the aim that the process used to manufacture Phase III materials (which will, one hopes, become the process used to make a licensed product) is shown to be at least validatable, if not actually validated.

All the analytical methods, at least for the finished product and the API, should be validated during this period as well.

**29.2.11.3 During Phase III.** The analytical methods applied to starting materials, other than the API, and to intermediates, should be validated during this period.

Cleaning validation work can also be done during this period, to ensure that a suitable cleaning process can be handed over to the routine manufacturing function at the appropriate time.

As for process validation, there is no requirement that this is completed by the time of submission of the Marketing Authorisation application. It must, however, be successfully completed by the time the product is placed on the market. Therefore, there is a case to be made for the completion of one validation run, prior to the submission, to verify both that the process is likely to be validated successfully and to verify that the validation protocols are appropriate. The remaining two (at least) validation runs can be carried out at a later date.

## **29.2.12 Batch Release**

This is one of the areas most affected by the introduction of the Clinical Trials Directive, 2001/20/EC. The concept of QP certification is well established for licensed products, and the directive introduces a similar requirement for QP release of IMPs. To be a QP suitable for the release of IMPs, one either has to meet the current requirements for a QP as spelled out in Directive 2001/83/EC, or have been actively releasing clinical trial supplies prior to May 2004. (In the UK, a minimum period of 6 months prior to 1 May 2004 has been imposed, together with certain other requirements). In addition, the UK regulations require that the application to be named as a QP based on experience gained before 1 May 2004 has to be submitted prior to 1 May 2006. The duties of the QP are set out in the Clinical Trials Directive and in the national legislation implementing the directive, as well as in Annex 16 to the EU GMPs, although parts of this latter may need to be modified. For example, there is mention of testing upon importation in Annex 16. This is a requirement for licensed products made outside the EU in a country with which a mutual recognition agreement is not in place, which is incorporated into directive 75/319/EC and its later successor 2001/83/EC. There is no explicit requirement for such testing of imported IMPs in 2001/20/EC. However, it appears at the time of writing that the different member states may take differing approaches, some requiring testing on importation, others not, while yet others will decide on a case-by-case basis, dependent on the justification offered by the QP.

## **29.3 OTHER ISSUES**

### **29.3.1 Active Pharmaceutical Ingredient Manufacture**

A fairly recent development has been the creation of internationally-harmonised guidelines for GMP for the manufacture of APIs, as ICH Q7A “Good Manufacturing Practice for Active Pharmaceutical Ingredients”. This has been incorporated into EU GMP as Annex 18. This is not currently enforceable under European law, but there are moves to change this, and to require compliance with this guideline in the manufacture of APIs. Control of API manufacture for

Clinical Trials use is set out in Section 19 of this guideline. This provides extensive guidance on what is required. In general the standards are similar to those one would expect to apply to the manufacture of drug product at a similar stage of development. The guidance is in some areas more detailed than that available for production of IMPs themselves and provides some useful insight into requirements for drug product manufacture as well. Some of the more challenging requirements are discussed below, with the extracts from the guideline given in italics.

### 29.3.1.1 Quality

*A quality unit independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.*

This is an important principle, but one which is likely to present some challenges. As stated above, approval or rejection implies an assessment of suitability for use, and under full GMP is done against a comprehensive specification. In the case of IMPs, detailed specifications are unlikely to be available due to the limited data on the synthesis and analysis of the active pharmaceutical ingredient.

*Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.*

The possible level of compliance with this requirement will depend on the nature of the raw materials used in the synthesis. This is recognised in a succeeding paragraph.

*Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.*

The very nature of developing new compounds for evaluation in drug development takes the synthetic process into new areas of chemistry in which conventional standards of characterisation of starting materials will not be possible.

*The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records or by other appropriate means. These documentations should include information on the use of production materials, equipment, processing and scientific observations.*

This seems to allow a suitable degree of flexibility while retaining the vital element of having a complete documentation record of what has taken place.

*Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration and, where appropriate, equipment qualification assures API quality during this development phase.*

This is very similar to the principles applied to product manufacture.

*While analytical methods used to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.*

The nature of the testing applied to active pharmaceutical ingredient for use in the manufacture of an IMP is worthy of discussion. In general, the vast majority of APIs for commercial production

are evaluated by high performance liquid chromatography (HPLC), using methods of exquisite sensitivity and resolution power. A basic HPLC method should be available for active pharmaceutical ingredient analysis for IMP use, but the normal degree of sophistication is rarely available. Additional more sophisticated testing should therefore be performed to assure product quality including  $^1\text{H}$  and  $^{13}\text{C}$  NMR, LC-MS and elemental analysis together with sulfated ash, organic volatile impurities (OVI), and any testing for any heavy metals used as catalysts at any stage of the synthesis. Melting point, normally by DSC, X-ray powder diffraction and IR spectra will provide further valuable information for later phases of development and are routinely performed in most companies.

Taken together, these tests provide both assurance of the nature and quality of the active pharmaceutical ingredient, and a suitable basis against which future batches can be evaluated. These tests should be applied not only to material used for IMP production, but also at earlier stages including GLP toxicology studies. Although not strictly within the scope of this chapter, the quality evaluation of active pharmaceutical ingredient for GLP use is just as important as testing for use in IMPs.

*A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.*

This is an extremely important requirement and yet one which is often overlooked. It is inevitable that the quality of active pharmaceutical ingredient will change with time during development. The general expectation is that it will improve. Analytical methods used to analyse the active pharmaceutical ingredient must also improve. For this reason, any regulatory submission including those made at the clinical trial stage should include a batch analysis table presenting all of the analytical data available on all active pharmaceutical ingredient batches manufactured. If the development reaches the stage of Marketing Authorisation, analysis of all batches used in toxicology will need to be compared with the analysis of the active pharmaceutical ingredient to be included in the commercial product. For this data to be meaningful, the analysis of the early phase batches should be done using the best method available and compared with the proposed commercial active pharmaceutical ingredient analysed using the same method. If no samples above the legally required minima (which cannot be used for such purposes) have been retained from the early phase materials, this is not possible!

The retained samples should be stored in such a way that their integrity is most likely to be maintained. In many cases, storage at low temperatures is advisable.

*Expiry and retest dating . . . applies to existing APIs used in clinical trials. For new APIs . . . (it) does not apply in early stages of clinical trials.*

Nevertheless in the opinion of the authors, stability data on the API to be used in any human study should be generated.

### 29.3.2 Phase One Material Manufacture – “Drug in a bottle”

Pressures on resources and timings are resulting in a new approach to the preparation of IMPs for use in Phase 1 – the so-called “drug in a bottle” administration. This is the extemporaneous preparation of a solution or suspension of the active pharmaceutical ingredient immediately prior to administration by staff in the Clinical Study Unit, using drug in a bottle provided by the study sponsor for the purpose.

Although attractive in some ways, there are numerous pitfalls in this approach. One of the most obvious is that it contradicts a *sine qua non* of the GMP, namely that the product is identified and assayed prior to administration. Using the “drug in a bottle” approach means that, at best, the

product is analysed after administration and at worst not at all. Such an approach reduces the administration to that used in animal testing. Further problems are that placebo matching using the “drug in a bottle” approach is much less straightforward, as the drug is in solution or suspension and so can be both seen and tasted.

A further issue is that, if the drug is administered as a suspension, there is sometimes doubt that a repeat administration under identical conditions could be achieved bearing in mind the limited characterisation of active pharmaceutical ingredient properties usually available for first administration. Establishing that a subsequent administration truly repeated the original experiment, despite using material with the same morphic form and particle size, could be highly problematic.

It is recommended that quality management issues surrounding this approach should receive considerable scrutiny from quality Personnel and sponsor alike. To quote Tolkien, “Short cuts make long delays”.

## **29.4 CONCLUSION**

Despite the difficulties and issues raised above, the general principles of GMP apply to IMPs, just as they do to licensed medicinal products. However, the specific application of some of the requirements requires more careful planning and control.

## CHAPTER 30

# Chemical Analysis

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### 30.1 INTRODUCTION

Materials used in the manufacturing and packaging of drug products must be of suitable composition and quality to ensure that the drug products possess appropriate quality properties throughout their shelf lives. These materials may include packaging components, formulation excipients, preservatives, the active pharmaceutical ingredient (API) as well as the final finished product. There is a set of quality specifications that each batch of material must meet to assure that the final drug product is effective and safe. This is accomplished by understanding what characteristics of each specific material is important in producing a final drug product that will meet appropriate identity, strength, quality and purity characteristics.

Quality characteristics are identified early in the product life cycle and approved by the regulatory authorities before the product is approved for distribution and use. Associated with each quality specification is a test method and specification that will allow evaluation of each specified quality characteristic. The test method must be designed and validated to ensure that accurate evaluation will be obtained on that particular material. If the test results obtained on any material do not meet the pre-established quality specifications, then that batch of material will be rejected. It is, therefore, of great importance that the procedures used to test all of the different materials consistently generate accurate results. To limit the size of this chapter, the focus will be primarily on chemical test methods that the quality control (QC) unit may perform on the finished drug product.

### 30.2 THE ROLE OF TESTING MATERIALS IN THE QUALITY CONTROL AND QUALITY ASSURANCE UNITS

The typical role of the QC department is to perform testing on the materials needed to manufacture and release the final drug product. Different groups within the QC unit may concentrate on specialised types of testing. These areas may include raw materials used for manufacture, packaging components, in-process samples, chemical testing, microbiological testing, *etc.* Some groups may specialise in product release or stability testing while others may focus on complaint and non-routine samples. The common requirements of all testing by the QC group is that samples are selected using a pre-determined sampling plan and evaluated using test procedures that have been approved by the regulatory authorities. All work must be performed by trained analysts using current good manufacturing practices and following the company's standard operating procedures.

The main role of the Quality Assurance (QA) unit regarding testing is to ensure that proper test procedures, equipment, company's standard operating procedures (SOPs) and current good manufacturing practices (cGMPs) are being followed. The QA unit will evaluate all information related to the acceptability of batches including the test results generated by the QC group, and make the pass/fail decision.

### 30.3 CGMP TESTING REQUIREMENTS THROUGHOUT A PRODUCT'S LIFE CYCLE

There are many types of specifications that each batch of material will be evaluated for that together as a package will determine if a batch is suitable for its intended use, that is all test results meet the limits of that material's specification. Failure of a batch to meet any one specification will cause rejection of the batch. No one specification will indicate the acceptability of a batch, but all work together and complement one another so that the quality determination can be made. Testing can be performed throughout the life cycle of a drug product, and sometimes the initial release specifications may be different from the end of life specifications.

The chemical reagents and excipients that go into the final product are tested for properties that will eventually be important to the quality of the final product such as strength, quality and purity. The active ingredient is thoroughly tested for relevant characteristics. In many cases chemical intermediates may be tested before the final drug substance has been produced. When the active ingredient is added to the other drug product formulation excipients, further testing may be required before the final form of the drug product has been produced. Before the drug product is packaged, additional physical and sometimes chemical testing may be performed. After packaging, the drug product will be evaluated before release to the market. Selected batches of each drug product will be placed in tightly controlled environmental conditions in all representative container closure systems and tested periodically throughout and past that product's expiry period to demonstrate that the stability characteristics of the product have remained acceptable over time. In Table 1, typical tests are listed that may be run at each stage of production.

**Table 1** *Typical tests that may be run at each stage of production*

<i>Excipient</i>	<i>Drug substance intermediate</i>	<i>Release for drug substance</i>	<i>In-process for drug product</i>	<i>Release for drug product</i>	<i>Stability for drug product</i>
Identity, physical description	Identity	Identity, physical description	Uniformity	Identity, physical description	Physical description
Potency	Potency	Potency	Potency	Potency	Potency
Purity	Purity	Purity	Physical characteristics	Purity	Purity
Heavy metals		Heavy metals		Moisture	Moisture
Residue on ignition		Residue on ignition		Organic volatile impurities	Physical characteristics
		Moisture		Physical characteristics	Dissolution
Moisture		Organic volatile impurities		Content uniformity	
Residual solvents		Physical characteristics		Dissolution	
Physical characteristics					



### 30.4 TRAINING REQUIREMENTS TO ENSURE THE PROPER EXECUTION OF TEST METHODS

The best of test methods may not yield accurate results unless the analyst using the method is properly trained. This training includes:

- (i) Basic cGMP procedures for an analytical laboratory
- (ii) Understanding of the basic principals upon which the method is based
- (iii) Laboratory techniques such as weighing, mixing, diluting, sampling, *etc.*
- (iv) Instrument set-up and operation
- (v) How to accurately carry out all of the procedures in each specific test method.

Training on the basic techniques and on the specific test method is normally demonstrated to the satisfaction of the trainer or laboratory supervisor and documented in each analyst's training log. Test results generated by an analyst are not used to evaluate samples for release or stability purposes until all appropriate training has been completed and the training records signed off.

### 30.5 LABORATORY REQUIREMENTS FOR CGMP TESTING

Since it is important to consistently generate accurate results in a cGMP laboratory, it is important to understand the influence that the laboratory environment can have in producing analytical error. A well-trained analyst using calibrated equipment and a robust test method can still generate inaccurate results unless the laboratory environment is conducive to accurate analysis. Some potential laboratory environmental factors that could lead to errors are listed below:

- (i) *Cleanliness* – Contamination of samples, standards, reagents, solutions, equipment, glassware, *etc.* can cause interference and inaccurate test results.
- (ii) *Environment* – Temperature fluctuation, high humidity, drafts, *etc.* can affect samples, instruments, physical, chemical and detection properties and may have effects on how a test procedure works. Samples and standards must be stored in a proper environment to assure their integrity.
- (iii) *Vibrations* – The accuracy of weighing which is the basis of most analytical methods can be negatively affected by vibrations. Some test results such as dissolution testing may also be affected by vibrations.
- (iv) *Calibrated equipment and glassware* – The accuracy of test results are dependent on accurate volume measurement and detector signal measurement. The grade of glassware required for a test is dependent on the nature of that test and its use.
- (v) *Distraction free environment* – The analytical laboratory must provide a workspace where each analyst can concentrate and focus on performing each step of each test with high precision and accuracy. Distractions of any nature may cause a procedural error that may go undetected and negatively affect the accuracy of the test result.

### 30.6 EQUIPMENT, COMPUTER SYSTEM QUALIFICATION AND VALIDATION REQUIREMENTS FOR THE TESTING LABORATORY

Today, most analytical test methods utilise sophisticated electronic equipment that is used to measure a signal produced by the presence of the analyte. The test result is then calculated using the quantitative measure of the detection signal magnitude. In recent years much attention has been focused on ensuring that the equipment used to make these measurements are of appropriate design, have been installed properly, are operating to design specifications, and have met pre-specified performance requirements. In addition to ensuring that the equipment is qualified

to perform the analytical measurements of interest, this equipment must be periodically calibrated. In some cases, performance checks are frequently performed between calibration points to provide better assurance that accurate measurements are consistently being made. Computers commonly process raw data into more useful information that is used in determining the magnitude of the sample and standard signal. Once the raw signals are transformed into more useful forms, the computer can perform further calculations to generate more meaningful results including a result that is consistent with the units found in that drug products specification.

The numerous and complex data manipulations and calculations that are part of the computer program must also be validated (see Chapter 37) to ensure that errors are not generated under the various possible scenarios that may occur during actual use. When the computer program is being designed and perfected this is often referred to as de-bugging a program. The testing goes beyond just determining if errors are generated in actual daily use, but all possible situations that could occur during the evaluation are anticipated and tested.

In addition to ensuring that test results that are generated are error free, there are also requirements that apply to a guaranteed audit trail being maintained. This audit trail should not be erasable and must be accessible to regulatory authorities so that they can determine if certain test data or results have been selected or rejected based on non-objective criteria. Thus, the requirements and testing performed to meet both technical and regulatory requirements today are very sophisticated and are designed to eliminate both technical errors and any inaccuracies that may occur through human intervention.

### **30.7 LABORATORY RECORDS, WORKSHEETS, NOTEBOOKS, LIMS**

Laboratory data are one of the key links to the final test result on which quality decisions will be based. The cGMPs cover not only how laboratory data are obtained, but also how they are recorded, checked, revised, archived, *etc.* The raw data may be handled from an analyst observing a reading and recording it onto a worksheet or into a notebook having the equipment perform to the measurement, performing calculations and transferring the results to a laboratory information management system (LIMS). Regardless of the specific way that the measuring, recording and calculating occurs, there must be a clear record of all raw data and how it is manipulated to generate a final test result. Raw data, worksheets, notebooks, computer files, test methods with calculations, *etc.* must be securely stored and be retrievable for auditing purposes.

The raw data should be directly captured in a system that is fully auditable and has a complete history of change when practical. Manual data collection must be entered directly into an official notebook or numbered worksheet and not recorded on a piece of paper and then transferred to the notebook. Notebooks and worksheets must have consecutively numbered pages and the analyst must sign and date each page. Someone with adequate knowledge must review the analyst's data and also sign that it has been checked. If there is a need to modify or delete an entry, then the original data must be maintained and a reason provided explaining why the revision was made. The person making the change must also sign and date the changes to the document. This applies to when the data is collected and/or transferred both manually and electronically. The calculations that were used to generate the final result from the raw data must be auditable and have been validated and this validation must be documented.

### **30.8 SAMPLING AND RETENTION OF SAMPLES**

Samples to be used for testing must be obtained by the procedure defined in the sampling plan. It is important that samples that are used for testing represent the whole batch. Enough samples should be taken so that if a new sample preparation is required because of some issue with the original test results, then the new preparation can be made from the original laboratory sample.

It is also important that if a homogeneity or uniformity sample is obtained, it represents an amount close to the unit dose amount for that product. In the case of individual dosage units like tablets or capsules, this is easily accomplished. In the case of pre-compression formulation blends, and liquid samples like suspensions, creams, *etc.* a target amount of sample is required for uniformity testing that is close to the unit dose amount that a patient would take.

Samples and solutions should be clearly labelled with all the required information to prevent sample mix-up. Sufficient samples of each batch of active ingredient and drug product should be stored at labelled conditions at least one year past the drug product's expiration date so that complete re-testing can be performed if necessary. Samples of each batch of drug product should also be pulled and examined annually to make sure that nothing out of the ordinary is happening. This examination is normally visual rather than chemical or microbiological testing. In addition, representative batches of each drug product are placed in tightly controlled environments so that the stability of all products is monitored with all appropriate stability indicating test methods. The number of samples, environmental storage conditions, sampling time points, *etc.* are determined by the nature of the sample and the study of interest.

### 30.9 REFERENCE STANDARDS USED FOR CGMP TESTING

Most test methods require that reference standards be used in the procedure in addition to the samples being evaluated. These well-characterised substances can provide both qualitative and quantitative information. Qualitative information may be needed each time the test is run. Reference standards are often used in chromatographic system suitability tests to provide peak shape, resolution, sensitivity, *etc.* information about the analytical system each day.

Identity methods will only use the reference standard for qualitative purposes. Some quantitative methods also depend on reference standards for qualitative information. For example, in chromatographic methods, the time that it takes a compound to pass completely through the column to the detector, that is the retention time may vary depending on the age and condition of the column, the exact mobile phase composition, column temperature, *etc.* Therefore, an absolute or even a relative retention time cannot be depended upon to predict the retention time of each analyte each time the method is used. Using a reference standard in the chromatographic method each time will allow the analyst to know which chromatographic peak was caused by which particular compound with high certainty.

For some analytical techniques such as ultraviolet spectroscopy, there may be no need for a qualitative assessment. In that case, the reference standard may be used for quantitative purposes only. A known concentration of a reference standard solution will produce a certain magnitude of detector response. The detector response per unit concentration for the reference standard can be used to determine the sample solution concentration, which will allow the potency of the sample to be calculated. In chromatographic methods, reference standards are used in the same quantitative way to obtain potency or impurity level information.

### 30.10 QUALITATIVE/IDENTITY TESTS

Qualitative methods are often referred to as identity tests. Identity tests indicate what materials are present rather than how much of a material is present. Since many materials may look alike to the eye and could possibly be mislabelled, it is important to have identity tests that can differentiate the material of interest from all other materials. Although most qualitative tests performed in QC laboratories are run to differentiate one compound or product from all others, some qualitative tests indicate what form a given compound is in. Examples of this include the differentiation of physical crystalline forms of solids to determining the enantiomeric form of molecules.

Identity tests are qualitative test procedures that can establish if the sample under study is in fact the substance of interest. The most important aspect of an identity test is that it is specific, that is it can differentiate the material of interest from other materials. Often some spectroscopic “fingerprint” will be used to confirm the identification of a substance along with a second confirmatory identification test. The most common primary or fingerprinting identity tests are spectroscopic techniques such as infrared, ultraviolet-visible, NMR, *etc.* spectroscopy. The most common supplemental technique for identity tests is chromatography where the retention time of the sample peak is compared to that of a known reference material when using the same chromatographic system.

### 30.11 PHYSICAL TESTS

There are several important types of tests that require testing physical attributes of samples. These physical properties may influence the elegance and performance of the product.

- (i) *Physical description* – A visual description is normally part of the material’s specification that sometimes has added identification benefit. A visual examination may detect excessive moisture, degradation, a manufacturing error and can differentiate one drug product presentation or strength from another.
- (ii) *Particle size* – Particle size is a characteristic that can affect the availability of the active ingredient to the patient. Sometimes this property is controlled indirectly by another test such as dissolution or it may be controlled directly. Inhaled drug products where the active ingredient remains as a solid such as a dry powder or an aerosol suspension commonly have particle size distribution specifications. Techniques to measure particle size range from direct visual measurement of particles using a microscope to some quantitative measurement that can be performed on the whole or fractions of sample collected according to particle size range.
- (iii) *Weight variation* – If the drug product meets certain requirements regarding minimum per cent weight composition for the active ingredient, then the uniformity may be assessed by simply weighing a specified number of individual units and then calculating the weight variability of those units.
- (iv) *Disintegration* – Many solid dosage forms such as tablets, capsules and even suspensions have dissolution or disintegration test requirements. The basic concept associated with this test is that a quantitative range of the active ingredient should be available to the patient (dissolved) within a certain time. Some drug products with highly soluble active ingredients only require that the tablets physically break down or disintegrate when placed in a specified solvent within a specified time period. It is assumed that if the dosage form disintegrates exposing the active ingredient to the solvent, the high solubility of the active ingredient ensures adequate dissolution and, therefore, availability to the patient.
- (v) *Other physical characteristics* – Test methods such as colour, crystalline form, fill volume, friability, hardness, specific gravity, *etc.* may be applied to certain types of dosage forms. Non-conformance to these types of product specifications may indicate some manufacturing defect that may affect the elegance, stability, availability or quality of the drug product.

### 30.12 MICROBIOLOGICAL TESTS

Most microbiological tests evaluate the presence or absence of potentially harmful microbes. They can also determine the efficacy of preservative agents, assure packaging integrity, evaluate sterility

using biological indicators and enumerate/identify environmental isolates to name a few. There are four microbiological chapters in the USP:

- (i) *Anti-microbial effectiveness testing* – The effectiveness of an added preservative agent is evaluated by inoculating the product with a known concentration of a designated test organism and determining the population of that organism after appropriate incubation intervals. The reduction or lack of increase in the numbers of inoculum determines the efficacy of the preservative.
- (ii) *Biological indicator testing* – Biological indicators are used to determine the effective performance of a sterilisation cycle designed to determine if an adequate temperature or exposure has been achieved to assure sterility of the material. The biological indicator, whether a paper strip or a contained liquid, is placed in the sterilising system such as an autoclave or ethylene oxide gas system and should demonstrate that the organisms contained are destroyed in a set period of time. A population determination is initially performed to verify the level of organism that is contained within the biological indicator.
- (iii) *Microbial limits testing* – Products are tested (raw material, API, and finished products) to assure that objectionable microbiological organisms such as bacteria, yeast, and mould are not present. The particular objectionable organisms are listed per USP, EP, JP, *etc.* Products can be tested by diluting and plating with several different types of agar. The product can be diluted, filtered and the filter placed on solidified agar. Product can also be diluted in an enrichment broth and tested by sub-culturing to differential/selective agars. These tests then require incubation and afterwards are checked for growth.
- (iv) *Sterility testing* – This testing is performed to ensure products purporting to be sterile are in fact sterile and comply with requirements set forth in the USP, EP and JP. Two methods are used for sterility testing: membrane filtration and direct inoculation. Aseptic technique is critical for this type of testing. Controls are performed alongside the testing of the product to ensure the sterility of the media, diluting fluids, *etc.* Sterility testing must be performed under aseptic conditions either in a class 100 environment or isolation chamber.

### 30.13 QUANTITATIVE CHEMICAL TEST METHODS

When the level of an analyte needs to be determined, a quantitative test method is required. This type of method not only indicates that the material is greater or less than the level in the specification, but measures exactly at what level this material is present. Potency methods are common examples of methods that need to be quantitative. Impurity methods for compounds that may increase throughout the product lifetime must be quantitative in nature including moisture and specific degradation products.

Previously, quantitative test methods were based on detecting a unique property of the analyte compound. Examples of these properties include acidic or basic functional groups, UV absorbing, electrochemical, complexation/reaction chemistry and solubility properties of the molecule. Although these test procedures were often very precise, these methods often suffered from lack of specificity. Other materials present in the sample with similar detection characteristics would contribute to the detection measurement and thus cause a high bias in the quantitation of the target material. Some of these non-specific quantitative test method techniques are still used today, but typically only used in conjunction with other specific test methods that will measure the levels of interfering compounds.

Many of the quantitative test methods that are used today are chromatographic-based methods. These methods physically separate the analyte compound from the other components in the formulation and/or impurities during the detection measurement process. Thus, any potentially interfering component will not be present in the detector cell when the analyte peak is being

measured. This separation is often performed by using chromatographic systems containing two phases such as solid–liquid or solid–gas, *etc.* The two phases and the other chromatographic parameters are selected to have the analyte spend a different percentage of its time in one of the phases compared to all of the other potential interferences. The liquid or gas mobile phase is normally pumped through the stationary phase that is packed onto a column. Eventually depending on the per cent of time that the analyte is associated with the mobile phase versus the stationary phase, it is eluted from the column into the detector cell where a quantitative measurement of the analyte is made.

Several common chromatographic techniques are summarised in Table 2. There are several different types of test methods used to evaluate materials that have different basic purposes. The differences here refer to the type of quality information desired and not to the type of technology used. A brief description of several of these basic types of test methods will be described below.

- (i) *Potency* – Potency tests are used to establish if the sample under study contains the correct amount of active ingredient. Samples are tested to determine if the amount of active ingredient present is consistent with the theoretical content or label claim plus or minus the tolerance specified in the acceptance criteria. Representative samples of the batch are quantitatively evaluated for the amount of active ingredient contained on average for each unit weight or dosage unit. Any batch that is sub or super potent, that is has potency outside of that listed in the product specification, must be rejected. The potency of batches is required to be within specification throughout its expiry period. The potency test method must produce accurate results in the presence of other compounds, some of which may be very similar to the analyte. This specificity requirement may be included in the potency test itself or may work in tandem with a specific impurity test that allows upto a specified amount of individual or total impurities. The potency of a drug product batch may at times be determined by calculating the average of the content uniformity test results.
- (ii) *Content uniformity* – Meeting potency requirements that is representative of the whole batch of drug product is necessary but not always sufficient. It is possible for a portion of some types of dosage forms to be over-potent and another portion of the batch to be sub-potent and still have an overall potency within specification. Content uniformity testing requires that multiple single units of these types of dosage forms be tested individually. The content uniformity specification allows for only so much variation among the single units tested and no single unit can assay outside specified limits. Another type of related test

**Table 2** *Several common chromatographic techniques*

<i>Technique</i>	<i>Mobile phase</i>	<i>Stationary phase</i>	<i>Pulling force</i>	<i>Detection</i>
Thin layer chromatography	Liquid	Solid particles	Mobile phase by capillary action	Visual, densitometry
High performance chromatography	Liquid	Uncoated or coated porous or non-porous particles	Mobile phase pumped through column	Ultraviolet absorption
Gas chromatography	Gas	Coated particles or thin films on column walls	Gas pressure	Flame ionisation electron capture
Gel electrophoresis	None	Gel bed	Positive or negative field	Visual, densitometry
Capillary electrophoresis	None	Liquid	Positive or negative field	Ultraviolet absorption
Gel permeation or size exclusion chromatography	Liquid	Porous particles	Mobile phase pumped through column	Ultraviolet absorption



involves the dose delivery systems. For example, an inhaler product may be required to deliver a unit dose of active ingredient that falls within a specified quantitative range. This unit dose delivery requirement is measured throughout the usable portion of the container and is evaluated throughout the product expiry period for some types of dosage forms.

- (iii) *Impurities* – Pharmaceutical products may contain several types of impurities that may arise from the manufacturing process, formulation ingredients, decomposition of the active ingredient or formulation ingredients, *etc.* Low levels of impurities are unavoidable and their presence in samples is acceptable if they are sufficiently low. Studies are performed during drug development to understand the side reactions and decomposition chemistry of the active ingredient so that the level of each potential impurity is minimal and can be monitored. Related impurity specifications are established for products to control the maximum level of related substances such as process impurities, enantiomers and decomposition products. Impurities that are not related to the active ingredient such as organic volatile impurities, heavy metals, non-volatile materials, water and extractables from the immediate packaging, *etc.* may also be listed in the product specification. Samples are tested for these compounds to ensure that the levels of impurities present do not exceed the specification levels before the product is released. Samples of representative batches are also routinely tested periodically throughout and past the expiration date of the product to ensure that the impurities that can increase over time do not exceed their upper specification levels.

Sometimes it is important to know that there is not more than a specified amount of an impurity in a sample, but it is not important to know exactly how much of this analyte is present. This situation allows for the use of a semi-quantitative pass/fail or limits test. No additional quantitative information is obtained other than the level is or is not above the maximum level in the material's specification. This often applies to a group of undesirable substances that are only safe when present at low levels and these levels are unlikely to change as the product ages. Heavy metals and non-volatile material detected in residue on ignition tests are common examples of these types of materials. Residual traces of a catalyst that was used in a reaction process or any single impurity that does not increase over time could also fall into this category. There is no need to know how close to the upper limit the analyte is or to test for these impurities throughout the sample lifetime. In the case where the degradation product levels may increase, a quantitative test is required and this test must also be used for stability evaluations.

- (iv) *Preservatives and formulation excipients* – Some product formulation excipients including preservatives are required to be present at specific levels to maintain the product's appropriate physical and/or performance characteristics. Some finished products are tested to determine if the amounts of these critical excipients are present at theoretical levels plus or minus the tolerance specified in the acceptance criteria.
- (v) *Dissolution* – It is necessary but not sufficient that the chemical compositions of some drug products are within the specified limits. When the active ingredient makes up only a small portion of the dosage unit mass or is not highly soluble in the dissolution media, then a dissolution test is required. A single dosage unit such as a tablet is placed in a dissolution bath containing a specified solvent and mixing apparatus. The sample is exposed to the specified amount of solvent at a controlled temperature and stirring rate. The dissolution media is normally chemically close to the stomach environment such as 0.1N HCl. The amount of active ingredient that is dissolved at the specified dissolution time period is measured. For controlled released products, the dissolution medium is sampled at several time points to ensure that the active ingredient is being released at an appropriate rate. The availability of the active ingredient in cream or ointment dosage forms can also be



determined using specified membranes to assure that the correct amount of active ingredient is available to the patient.

### 30.14 STABILITY TESTING IN A CGMP LABORATORY

Stability test methods must be developed that will monitor the product's characteristics that may change over time. These may be physical, chemical or microbiological properties of the product and are dependent of the specific product type. The stability testing should evaluate if the product maintains adequate potency, quality and purity throughout its expiry period when stored under label conditions. Characteristics that will not change during product aging but must be evaluated for product release such as the content uniformity of tablets or quantitating manufacturing process impurities, *etc* can be eliminated from the array of tests used for stability testing.

Extensive stability testing is required before an expiration period can be assigned to a new drug product. For approved drug products, changes in the manufacturing process, product formulation or packaging would require samples to be evaluated as described by the stability testing protocol. Although the stability of a drug product may have been thoroughly investigated during development with stability indicating methods and found to be stable, some subtle changes in the manufacturing process, equipment, packaging materials, raw materials or excipients could cause decreased stability. Therefore, ongoing routine stability testing must be performed on representative batches of drug products produced each year regardless of a good stability history.

### 30.15 NON-ROUTINE SAMPLE TESTING

There are some sample types that must be evaluated that may require a different set of test procedures and that may be treated differently than routine release or stability samples. Often a special group of analysts evaluate these types of non-routine samples since unlike routine testing, each sample and situation may require special consideration. Several types of non-routine sample evaluation are discussed below.

- (i) *Complaint samples* – Samples are sometimes collected which were associated with a customer complaint. These complaints may be quite different from each other including lack of effectiveness, product appearance, taste or smell, and adverse reactions. Normally there are model SOPs that provide guidance on what testing to perform depending on the sample type and complaint. Deviations from the model protocols can occur on an as-needed basis with justification. Potency testing may be performed on ineffective complaint samples where purity testing may be performed on samples that are thought to be degraded or contaminated.
- (ii) *Security samples* – Sometimes samples come back to the manufacturing facility that may involve some suspicious activity such as contamination or being produced by a counterfeit source and passed off as brand name product. These samples often require special testing in addition to routine testing to understand their true nature. Often extensive sophisticated testing must be obtained on a very limited amount of available sample. The accuracy of these test results is important not only to understand the sample characteristics, but may also end up being used as evidence in a legal case.
- (iii) *Process investigations* – Atypical or out of specification (OOS) results are sometimes obtained on samples that would indicate that something might have gone wrong with the manufacturing process. Another possibility of the cause for atypical results being generated for a batch is that the manufacturing process may not be robust. The manufacturing investigation may require that samples be collected according to an investigation protocol to determine the possible root cause for these atypical results. Appropriate conclusions to

prevent these problems from occurring in the future are dependent on the accuracy of these results.

### **30.16 DEVELOPMENT AND VALIDATION OF TEST METHODS FOR A CGMP LABORATORY**

Before a test method is applied to obtain qualitative, quantitative or performance information about a sample, the test method must be designed and then optimised around the specific sample type and the required information. If a drug product test method is being developed, then the formulation excipients have to be considered so that their presence do not interfere with the analyte signal.

The most common and often best way to eliminate one substance interfering with another when quantitating a multi-component sample is to physically separate the signal producing substances before measuring their individual detection signals. This is often accomplished by chromatography where there are two opposing forces attracting all of the different substances in a sample. Eventually all components should be pulled through the detection area where the detector response is proportional to the amount or concentration of the analyte. After a test method has been developed and optimised for a specific application, it must be validated to evaluate if it is suitable for its intended use. Depending on the particular application, methods may be validated for traits like specificity, linearity, precision, accuracy (recovery) and sensitivity over the concentration range of interest (see Chapter 21). The goal is to develop an efficient method that will consistently generate accurate results even when small changes in equipment, reagents, method parameters and analyst's techniques are introduced. Method validation is discussed in detail in Chapter 36.

### **30.17 TRANSFER OF NEW TEST METHODS INTO A CGMP LABORATORY**

Normally, new test methods are developed outside of the group that will be routinely performing them. In such cases, the new methods need to be formally transferred to the new group before they are used to evaluate samples. A method transfer protocol should be prepared that describes the experimental procedure and acceptance criteria that will be used to determine if the receiving laboratory can apply the new method in their laboratory and achieve accurate and precise results. The receiving laboratory will also evaluate the new test method to determine if it is suitable for its intended use.

A typical method transfer exercise would normally start with the laboratory that developed and validated the new method, that is the validation laboratory, sending the new method procedure to the receiving laboratory along with the method validation report. The validation analysts would then provide the receiving group with any training on the new method as needed. Once the receiving laboratory felt comfortable with the new method, analysts from both laboratories would each prepare and evaluate replicate sample preparations of a specified number of samples from common batches of product. The results from each laboratory would be compared to each other and to the acceptance criteria in the method-transfer protocol. If the results meet the acceptance criteria and if the receiving laboratory agreed that the new method was suitable for its intended use, then the exercise would be documented in a method transfer report. The receiving laboratory could then start evaluating release and stability samples with the new method once the regulatory aspects of employing a new test method are met.

### **30.18 EVALUATING DAILY TEST METHOD SUITABILITY**

A good method validation exercise should provide evidence that the test method in question not only is capable of generating accurate results, but also that the method is robust, that is that it

**Table 3** *Examples of system suitability tests*

<i>System suitability parameter</i>	<i>Typical wording in test method with a typical acceptance criteria</i>	<i>Method parameter tested</i>
Resolution	The resolution between two peaks is at least 1.5	Column, mobile phase
Tailing	The maximum tailing factor of a specific peak is not greater than 1.7	Column, dead space, mobile phase
Retention time	A specific peak should elute between a specific retention time window, <i>e.g.</i> 8.0–10.0 min	Column, mobile phase
Precision	The precision of detector response of a specified peak for replicate injections of a specified solution is not greater than 2.0% relative standard deviation	Injection volume and flow rate precision
Sensitivity	Able to detect and quantitate a specified peak, <i>e.g.</i> down to 0.05% level	Lamp and detector cell, column
Standard check	The response factor of standard preparation A must match that of standard preparation B within $\pm 1.0\%$ of the mean	Analyst error weighing, mixing, diluting

should continue to consistently generate accurate results when used in many different laboratory environments over time. The method validation exercise is extensive and takes a long time to perform but cannot guarantee that the test method will generate accurate results each time the method is employed in all laboratories in the future. Some factors that could cause inaccurate results include: column degradation, mobile phase composition problems, reagent quality problems, detector lamp deterioration, dirty detector cell, equipment problems such as excessive dead volume, injector repeatability, mobile phase delivery and instrument set-up error such as gradient profile, injection volume, analytical wavelength, flow rate, *etc.* The use of a different brand or model of equipment can sometimes have a negative affect on the chromatography, especially for gradient systems.

The way to ensure that the analytical system will generate accurate results for each chromatographic run without repeating the whole method validation exercise is to select several relatively short procedures that will challenge the analytical system. These challenges or experiments are called system suitability tests. The name is very descriptive of their purpose. These tests can quickly reveal if the analytical system is suitable for its intended purpose each time that the test method is used, usually once a day. Some system suitability tests will even detect some analyst errors. The method parameters that are checked during system suitability are selected for each test method based on sample and analytical technique and are written into the test method procedure. Some system suitability tests are evaluated throughout the chromatographic run in case some problem arises sometimes during the testing of samples. Examples of system suitability tests and which test method parameter they give information about are contained in Table 3. Each system suitability test must also have an acceptance criterion associated with it so that an objective pass/fail decision can be made.

The system suitability tests allow the analyst to evaluate if the analytical system is operating normally before test results are generated on the sample to be evaluated. This practice should avoid OOS results being generated due to the analytical system not operating properly.

### 30.19 CHANGES TO METHODS USED IN CGMP LABORATORIES

Sometime it is necessary to modify or replace a test method to consistently generate accurate results or to make the testing more efficient. When test methods are enhanced or re-developed, the modified or new test method must be re-validated. A re-developed or new test method must be fully

validated. A modified test method must be re-validated for each parameter that could be affected by the change that was made to the method. Thus a modified method would require a partial validation exercise that would supplement the original method validation package. Depending on the nature of the method modification and the regulatory agency's requirements, the validated modified test method may or may not be used to evaluate marketed samples before being approved by the regulatory agencies. The modified test method and the validation documentation must be sent to and approved by the regulatory agency before it can become the new regulatory method. New or modified methods and the validation package may also be sent to Pharmacopoeial agencies to be considered for inclusion, or to supplement or replace the current Pharmacopoeial method.

### 30.20 PHARMACOPOEIAL METHODS – METHOD VERIFICATION

When a new drug substance or product is first approved and introduced to the market, the product is normally protected by a patent and the production is controlled by the company holding the patent. The official regulatory test methods are those approved in the innovator's regulatory applications. Later in that product's life, the patent protection will expire and other manufacturers may apply to produce and market the product. There are agencies responsible for setting the testing standards for the off-patent drug substances and products. The required tests, test methods and acceptance criteria for these materials become the regulatory methods, although the innovator company is also obligated to meet the requirements in their original application.

The Pharmacopoeias provide chapters on the general background information about many test methods and how they should be performed. Specific directions for each specific drug are provided when a universal procedure is not adequate. Universal methods include heavy metals, residue on ignition, moisture determination, *etc.* Drug-specific methods include potency, purity and quality methods like dissolution testing on drug products.

Since the innovator's synthetic route or drug product formulation may be different from that of a generic firm's, Pharmacopoeial methods need to be verified for the generic company's drug substances and products. The methods supplied to the Pharmacopoeias although fully validated for the submitter's products may not be suitable for a different manufacturer's material. Different synthetic routes may produce different process impurities and degradation products that must be controlled in the drug substance or product. Different drug product formulations and excipients may also cause a different degree of interference or recovery of analytes that could cause significant analytical error. Each manufacturer must perform sufficient method verification evaluation to assure that accurate results will be obtained when testing their samples by the Pharmacopoeial test method. Method verification is normally the subset of method validation experiments needed to demonstrate that accurate results will be obtained when using a specific synthetic route or product formulation.

### 30.21 LABORATORY ERRORS, SOURCES, AVOIDANCE, IMPACT, OOS RESULTS, LAB INVESTIGATIONS

An OOS result may be generated because of two general reasons. First, the sample may not be of sufficient quality to meet the product specification. In this case it is desirable that the sample fails since something went wrong in the manufacturing process and the product is unfit for the market. Secondly, the possibility that the product was manufactured properly, but a test result was generated that did not reflect the true nature of the sample. In this case some analytical error occurred that was responsible for the OOS result rather than the quality of the sample.

There will always be some level of error associated with analytical measurements. One key to consistently generating accurate test results is to keep measurement errors to a very small magnitude so that these errors do not significantly affect the test result. For example, if the error in a weighing measurement can be kept below 0.1 per cent of the magnitude of the actual weight,

then this amount of error is considered acceptable since it should not influence the decision concerning the acceptability of the sample. Similar situations apply to volume, mixing, detection signal, *etc.* measurements. Factors that can contribute to significant analytical error include:

- (i) *Laboratory conditions* – vibrations, drafts, temperature and humidity conditions, cleanliness, *etc.*
- (ii) *Reagent quality* – improper grade, degraded reagents, moisture content, contamination, *etc.*
- (iii) *Equipment* – improper grade, size, calibration, physical problem, cleanliness, *etc.*
- (iv) *Instruments* – improper qualification or calibration, working order, cleanliness, *etc.*

Procedures should be in place to avoid analytical error from these sources. Another set of potential sources of analytical error comes from the analyst. Some potential causes of analyst error include:

- (i) Not following the correct procedure – solution preparation, instrument set-up, over looking potential problems instead of stopping the test to investigate further, *etc.*
- (ii) Poor laboratory technique – weighing, dissolving, diluting, mixing, pipetting, *etc.*
- (iii) Careless errors – size, type condition, cleanliness of glassware, and reagents, integration of chromatographic peaks, *etc.*

These types of errors are often difficult if detected when time has passed after an OOS result has been generated. Selecting the right person with the right attitude for the job, providing proper training and continuous support including a distraction free and unstressful working environment is essential in minimising analyst error.

Another potential source of analytical error comes from the test method itself. If the test method was not properly designed, optimised and validated, it may not consistently provide accurate results under even optimum conditions. The test method may lack one or more of several properties that could contribute to analytical error. Different analytical techniques have different requirements, so the list below is a general one.

- (i) *Selectivity* – The ability to detect only the analyte and not any other component that may be present in the sample or in the sample solution.
- (ii) *Precision* – The tightness and lack of scatter of results.
- (iii) *Linearity* – The direct relationship between the amount or concentration of an analyte and the detector signal produced. The linearity plot should normally have a small *y* intercept.
- (iv) *Recovery (accuracy)* – The ability to detect all of the analyte and have the detector response of the analyte be the same in both the sample and the standard.
- (v) *Sensitivity* – The ability to accurately detect and quantitate low levels of analyte when this is required.
- (vi) *Robustness* – The insensitivity of the method's ability to generate accurate results when small changes occur in test conditions and parameters.

The list of method requirements above is the same as for method validation. In addition, it is important that the analyte concentration be in the working range of the method. The range of a method is defined as the upper and lower analyte levels where it has been demonstrated that the method generates accurate results. If the analyte concentration is outside of the range, a method may generate inaccurate results.

### **30.22 ANALYTICAL TESTING REGULATIONS AIMED AT ENSURING OBJECTIVE EVALUATIONS – BARR DECISION**

In the early 1990s, a high profile US court case involving the Barr Laboratories addressed a situation where biased selection of test data was alleged and a large court case resulted which set

a strong precedent for the whole pharmaceutical industry. The outcome of this case was that the data/results that are generated from testing sample quality must be treated using specific rules. No data should be destroyed and all data should be accessible to regulatory audits. The computer programs used to handle analytical data must be considered in the sample quality decision. One must not select only certain passing results or perform additional testing and then average failing or OOS results with replicates of passing results to obtain a passing average and then not deal with the OOS result or the root cause.

Regulatory guidelines coming out of the Barr case and many other related incidents are focused on ensuring objectivity when evaluating the suitability of a sample for its intended use. These guidelines include: (1) considering all results obtained on each sample, (2) keeping all results and records generated on each sample and (3) having appropriate pre-defined procedures for testing regimes that do not allow the gathering and averaging or ignoring unwanted data or results in order to meet a release or stability specification. The enhanced audit trail requirements had a direct effect on record keeping and especially had a huge impact on electronic records. In the United States, for example, the Code of Federal Regulations that address this topic 21 CFR Part 11 was revised to better ensure that fraud associated with selection of passing data over failing data would be eliminated. The new much more strict approach affected instrument manufacturers, software program companies as well as the analytical testing sites.

Besides dealing with the collection, storage and audit trails for data, new guidelines were established for incidences where an OOS test result was generated. When an unexpected OOS result is generated, the supervisor must be notified and a preliminary investigation carried out according to a pre-established protocol (see Chapter 21). The purpose of this preliminary laboratory investigation is to determine if an obvious analytical determinant error had occurred during the testing procedure causing the aberrant result. If a determinant analytical error was discovered that would explain the OOS result, the investigation would be documented including the corrective action and the sample would be re-tested to determine if the sample met current specifications or not. If a clear determinant analytical error was not discovered in the preliminary laboratory investigation that would explain the OOS result, then an expanded investigation should follow. The expanded investigation would include a manufacturing investigation and an expanded laboratory investigation (see Figure 4, Chapter 21).

The expanded laboratory investigation requires a protocol to be issued before any additional laboratory work is started. This protocol should be based on the current general regulatory principles and guidelines that have been established specifically for this type of investigation. Once laboratory work has begun, the laboratory investigation protocol should be followed without deviation and the protocol should not be revised to allow for additional testing. A simplified version of a typical outline of possible actions to be taken in an expanded laboratory investigation is shown in Table 4 along with a brief rationale. An HPLC assay procedure for a solid dose drug product will be used for this example.

**Table 4** *Typical outline of possible actions to be taken in an expanded laboratory investigation*

<i>Laboratory action</i>	<i>Rational-challenge</i>
Re-inject contents in original HPLC vial	Injector, or other equipment malfunction
Mix original working solutions and re-inject	Working preparation originally not fully dissolved or mixed
Re-prepare working solution from original laboratory sample	Weighing or other stock solution preparation error
Re-sample and repeat assay procedure	Sampling error that resulted in a non-representative sample being tested. This is usually not allowed



If an expanded laboratory investigation is performed, the results generated in the investigation must “overwhelm” the original OOS result if no clear determinant error is discovered. This requires significantly more replicates of testing in the laboratory investigation exercise compared to the original testing that generated the OOS result. This requirement is a result of past instances where subjective data or result selection had occurred for monetary reasons rather than trying to accurately assess the quality of the product.

### **30.23 CONCLUSION**

Testing is required for materials used and produced in the pharmaceutical industry to determine if these materials are suitable for their intended use. The tests, methods and specifications that are developed based on the characteristics of each material and the properties required to produce a high quality product. There are many cGMP requirements that must be applied in the analytical laboratory since there is potential for analytical error to occur. If cGMP rules are consistently applied, the analytical results generated on samples can be relied on to make good quality decisions.



# Good Manufacturing Practice for Sterile Products

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## 31.1 GENERAL

First, an important statement of fundamental principle: good manufacturing practice (GMP) is not merely a codified set of official guidelines or regulations (as in “the GMPs”) promulgated and enforced by one or other of a number of regulatory bodies of varying degrees of expertise and competence. Its objective is not to satisfy, gratify or placate these bodies, rather its true and only meaningful objective lies in ensuring “. . . the safety, well-being and protection of the patient”.<sup>1</sup> This is true for the manufacture of all categories of medicinal, drug, pharmaceutical or other health care products. It is most emphatically, most crucially true for the manufacture of *sterile* medicinal products. These products are among the most difficult to manufacture according to appropriate quality standards. They also have the potential, through faulty manufacture, to be the most hazardous to patients.

Sterile products are notably different from other, non-sterile, health care products. The difference lies quite simply and obviously in the fact that they are, or are at least *intended* to be, sterile. This predicates manufacturing, control and quality requirements additional to those that are relevant to non-sterile products. The same quality and GMP considerations that apply to non-sterile products apply equally well to sterile products. But the attainment and maintenance of the sterile state imposes extra quality assuring demands. That is, the special requirements (ethical and professional as well as regulatory) for sterile products manufacture are *additional to*, rather than separate from, those that apply to health care products in general. Worldwide, most official statements on GMP, with perhaps the surprising exception of the US drug products “cGMPs” (21 CFR Parts 210 and 211), have substantial separate sections on sterile products. The “Sterile Medicinal Products” Annex of the EC GMP Guide<sup>2</sup> is the largest single section in that publication.

### 31.1.1 What Does “Sterile” Mean?

It is surprising that so important a word, so central a concept, as “sterile” (or “sterility”) has been so ill-defined and has met with such woolly ambiguity and equivocation in the various attempts that have been made to define it. (For a detailed analysis of this problem, see Sharp.<sup>3</sup>)

A totally unambiguous and unequivocal definition appeared in the 1983 edition of the British Guide to GMP (the “Orange Guide”)<sup>1</sup>

*Sterility: The complete absence of living organisms. [Note: The state of sterility is an absolute-There are no degrees of sterility]*

There have, however, been those who seem to find such a definition *too* uncompromising – and who prefer a concept of a state of “near . . .” or “almost . . .” sterility, where apparently the odd organism, here and there, is acceptable. The first official statement along these lines appeared in an amendment to the Nordic Pharmacopoeia in 1970:

*“Sterile drugs must be prepared and sterilised under conditions which aim at such a result that in one million units there will be no more than one living micro-organism”.*

(Nordic Pharmacopoeia 1970)

This Nordic definition set a pattern for a number of other “one-in-a-million-is OK” definitions. The US Pharmacopoeia (USP) XXI, for example, declared

*“(It is) generally accepted that . . . injectable articles or . . . devices purporting to be sterile . . . (when autoclaved) attain a  $10^{-6}$  microbial survivor probability, i.e. assurance of less than one chance in a million that viable organisms are present in the sterilised article or dosage form”.*  
(USP XXI)

The British Pharmacopoeia (BP) in 1988 adopted a similar (but note, only an *approximately* similar) stance, in considering sterility to be

*“... a theoretical level of not more than one living microorganism in  $10^6$  containers in the final product”.*

The potential problems (for patients) need to be considered before any unquestioning acceptance of such definitions. Consider, for example, a large volume parenteral (LVP) infusion. As real life events have tragically illustrated, in such products even normally non-pathogenic organisms can kill.<sup>4</sup> In many such products, one organism today can become many millions tomorrow. Over 100 million units of LVP solutions are administered annually throughout the world. Is it really acceptable that one in every million of those may contain organisms?– If it is, then we must also be prepared to accept 100+ unnecessarily dead patients per year.

However, more recent editions of USP and BP have evidenced a degree of backing away from the “less-than-one-in-a-million” position, possibly as a result of a dawning realisation of the potential practical consequences of adopting such a position. For example, the BP 2000 (Appendix XVIII) unequivocally states “Sterility is the absence of viable organisms” and adds

*The sterility of a product cannot be guaranteed by testing; it has to be assured by the application of a suitably validated production process . . . Failure to follow meticulously a validated process involves the risk of a non-sterile product or of a deteriorated product . . . It is expected that the principles of good manufacturing practice (as described in, for example, the European Community Guide to GMP) will have been observed in the design of the process including, in particular, the use of:*

- *qualified personnel with appropriate training*
- *adequate premises*
- *suitable production equipment, designed for easy cleaning and sterilization*
- *adequate precautions to minimize the Bioburden prior to sterilization*
- *validated procedures for all critical production steps*
- *environmental monitoring and in-process testing procedures.*

***Wherever possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen. (Author's emphasis)***

Later in this same Appendix (XVIII) the BP adds

*“The achievement of sterility within any one item in a population submitted to a sterilisation process cannot be guaranteed, nor can it be demonstrated .... The SAL (Sterility Assurance Level) for a given process is expressed as the probability of a non-sterile item in that population. An SAL of  $10^{-6}$ , for example, denotes a probability of not more than one viable microorganism in  $1 \times 10^6$  sterilised items of the final product. The SAL of a process for a given product is established by appropriate validation studies”.*

Space will permit only the quotation of just two further examples of differing “definitions” of sterility:

*“Out of a batch of one million units only one container may contain an organism (Statistically maximally 3 at a 95% confidence level)”.*<sup>5</sup>

And

*“STERILITY is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia”.* (EC GMP Guide)<sup>2</sup>

With the first clause of this EC definition, there can be no argument. Unfortunately, this statement is totally undermined by the immediately following implication that the so-called sterility test has relevance to the establishment of a state of sterility throughout a batch of product, which is, of course, nonsense, and dangerous nonsense at that.

Sufficient examples have been given (and there are others, see Sharp<sup>3</sup>) to demonstrate a range of variable (and indeed, often ambiguous) views on what is meant by the word “sterility”. There can be no more crucial quality characteristic than the sterility of, say, a parenteral product; yet just precisely what “sterile” *means* seems to have not been entirely clear in the minds of a number of pundits. In many statements on the subject, there is an element of compromise. Sterility tends to be regarded by some, very wrongly, as a *conditional* rather than an *absolute* state.

What is the problem? Why this indecision and ambiguity over so fundamental an issue? The answer is a very simple, albeit philosophical, one. It is that there is a *fundamental flaw* at the heart of much thinking and writing about sterility, and *that flaw resides in a confusion between the nature of a concept or a state, and the probability of the existence of that state.*

The point was well made in an insufficiently noticed paper by Brown and Gilbert<sup>6</sup>:

*“The concept of sterility is absolute. Whether or not a product is sterile is inevitably a matter of probability”.*

If this distinction were universally noted and adopted, the problem would cease to exist. The *only possible* definition of “sterility” is the uncompromised, unconditional and absolute one given in the UK Orange Guide, 1983. The question of the existence of such an absolute, negative state must, inevitably, be a matter of probability, not of absolute certainty, and there is nothing new or odd about that. This does not preclude our *aiming* to achieve this (or any other) absolute state. In the case of *sterility*, our concern should be about whether we have in fact achieved that state at an acceptable level of probability, and it is not unreasonable to suggest that what may be regarded as an acceptable level of probability could well be considered to vary according to circumstances.

Compare, for example, two different types of terminally heat-sterilised product:

- (i) A small volume (say, 0.5 or 1.0 mL) injection of a *non*-growth supporting liquid, intended for intramuscular or sub-cutaneous injection – and –
- (ii) An LVP, say 1 L of (growth supporting) dextrose/saline solution for intravenous infusion.

There can be no question that both should be sterile. However, one might well consider that the *level of assurance of the probability of attainment of that state* is more critical in the latter than the former.

### 31.1.2 Sterilisation – Fundamental Concepts

The process of sterilisation is often spoken of as if it were one single discrete type of operation. This is just not so. The various different methods of sterilisation are indeed very different one from the other: different in underlying theory and concept, in technology and in the advantages/disadvantages and potential hazards that each method represents. Each method needs to be operated and supervised by persons with a full understanding of, and experience of, that particular method and not merely of “sterilisation” in general. It is hardly an exaggeration to state, *e.g.* that the technological difference between the manufacture of sterile products using say (a) steam sterilisation and (b) filtration with aseptic processing is as great as, if not greater than, the difference between the manufacture of tablets and the manufacture of ointments.

There are two distinct, basic approaches for making a sterile product:

- (i) Filling and sealing the product into its final container and then sterilising it (*terminal sterilisation*).
- (ii) Sterilising a product at some earlier stage, before it is filled or packed, and then carrying out further processing and filling into sterile containers, using *aseptic* techniques and taking *aseptic* precautions.

It is generally considered that, if possible, it is best to use a terminal sterilisation process. This is simply because if the product is sterilised when securely sealed in its container it will remain sterile until the container is opened, broken or punctured in some way. When working with an unsealed sterile product, there is always a risk of re-contamination. Although that risk can be greatly reduced if proper care, with the application of modern technology, is taken, it can nevertheless be never entirely eliminated. That is why most experts and regulatory authorities agree that, where it is possible, products should be terminally sterilised. Sometimes this is not possible, for example when a product is not able to withstand a terminal heat-sterilisation process.

In addition to the obvious objective of making sterile products, which are *in fact* sterile, the products are also required, in many cases, to be free of particles and of pyrogens (or “bacterial endotoxins”). The attributes of freedom from organisms, non-viable particles and pyrogenic substances may be said to be interconnected. (Air-borne microorganisms are frequently associated with non-viable particles and pyrogens usually originate from the cell walls of Gram-negative bacteria.)

Another fundamental point, which is relevant to all types of sterilisation, is that *sole reliance cannot be placed on the sterilisation process alone, in isolation, to achieve sterility*. Much depends on

- The microbial condition of the materials, or articles, as they are presented to the sterilisation process
- On how they are prepared and handled *before* the actual sterilisation, by whom and under what conditions
- On the pre-established validity of the sterilisation process itself

- On the careful control of that process during the sterilisation and
- On what happens after the sterilisation process to confirm its efficacy and to prevent product re-contamination

The fragile fallibility of the so-called “Sterility Test” as a weak support in the assurance of sterility is so universally acknowledged that it requires no further emphasis. It is the very fact of the lack of any meaningful end-product test to demonstrate the sterility of a batch, which necessitates more disciplined approaches and higher orders of care and attention. Crucial to success are

- The *people* involved and their *training*
- The *premises* used and the *environmental standards* therein
- The *equipment* and its *commissioning/cleaning/sterilisation*
- The quality of the *materials* used (including *water*)
- *Validation* of the sterilisation process
- *In-process control* of the process and *in-process control* of the manufacturing environment.

## 31.2 PREMISES FOR STERILE PRODUCTS MANUFACTURE

### 31.2.1 Clean Rooms

The concept and design of clean rooms was first developed (in the early 1960s) for the microelectronic and aerospace industries. In these industries, it is important to protect microelectronic components against even the finest particles. Viable contaminants, as such, are of no special significance to microcircuits, only in so far as bacteria, *etc.* are themselves particles.

A clean room, as originally conceived, may be defined as follows:

*A clean room is an enclosed space with quantitatively specified control of:*

- *Particles*
- *Temperature*
- *Pressure*
- *Humidity*

*constructed with non-porous surfaces which are easy to clean and maintain, with controlled access via air-locks, and operated in accordance with procedures designed to keep contamination below a defined low level.*

Because of this origin in industries where product *sterility* is not the aim, classifications of the various classes of clean room are usually based upon the number and size of the particles (purely as *particles*) permitted per unit volume of the air in the room. Many published clean room standards also have specifications for humidity, temperature, lighting and air pressure. It was only later that the pharmaceutical and related industries adopted the concept, and then added to it certain permissible levels of microbial (or viable) contamination. Even so, a lot of what is said and written on this subject still sounds or reads as if it were based on a premise that it is the inanimate particles that are crucially important. In fact (all other things being equal), the presence or absence of *viable* contamination in, say, a parenteral product is a quality and patient safety issue which is even more critical than the presence or absence of non-viable contamination. It has to be said, however, that although there has been a lack of convincing demonstration of a direct linear relationship between the numbers of non-viable and the numbers of viable particles in a given volume of air, it is entirely reasonable to suppose that where there are low levels of non-viable particles there will

concomitantly be low levels of microorganisms. Air-borne microorganisms are most characteristically to be found associated with particles or droplets.

The unit of measure used to define clean rooms is the micrometre (0.001 mm), very commonly termed a “micron”. The first official published standard for clean rooms was the US “Federal Standard 209: Clean Room and Work Station Requirements, Controlled Environment”. This standard has gone through a number of revisions over the years since the 1960s – 209B, 209C, 209D and 209E, but the basic idea behind the US classification has remained the same. It is based on permitted numbers, per *cubic foot* of air, of particles of a size 0.5  $\mu\text{m}$  and larger.

There are three classes of US Federal Standard 209 Clean Room, which are particularly relevant to sterile products manufacture: class 100, class 10,000 and class 100,000 (see Table 1).

This US standard defines a number of other clean room parameters and conditions, such as temperature, humidity, air pressure, operator clothing and behaviour, and the instruments and devices to be used to measure and count particles in the air, but to date, it has made no reference to permitted levels of microorganisms.

Following the lead given by the US Federal Standard 209, a number of national and other bodies have produced standards for clean rooms, in essence very like the US standard, but with changes in the nomenclature used for the various classes, or *Grades*. For example, in 1976, British Standard No. 5295 “Environmental Cleanliness in Enclosed Spaces” was published. This defined four main classes of clean room. In sterile products manufacturing areas, normally only the first three of them are of interest or concern, *class 1*, *class 2* and *class 3*.

While at first sight these may look different, they are (respectively) closely similar to the Federal Standards – *class 100*, *class 10,000* and *class 100,000*, with, in British Standard 5295 the permitted number of particles in each class expressed in terms of a cubic metre of air, not per cubic foot. The BS 5295 (1976) figures for the three classes are shown in Table 2.

In 1989, a revised version of BS 5295 was issued with the various classes designated by letters rather than numbers, and the current edition of the Federal Standard (209E) has “gone metric”, and expresses the numbers of particles permitted, in each class, in terms of a cubic metre, while still retaining the old per cubic foot basis. Thus, “Class 100” is now also expressed as “Class M 3.5” (note: “M” here stands for “metric” and not “microbial”).

Table 3 shows how the standards so far discussed, plus some others, relate more or less to one and other.

**Table 1** *US Federal Standard 209E – maximum permitted number of particles per cubic foot of air in room*

Class	Particle size	
	$\geq 0.5 \mu\text{m}$	$\geq 5 \mu\text{m}$
Class 100	100	0
Class 10,000	10,000	65
Class 100,000	100,000	700

**Table 2** *BS5295 clean room standard – maximum permitted number of particles per cubic metre of air in room*

Class	Particle size			
	$\geq 0.5 \mu\text{m}$	$\geq 1.0 \mu\text{m}$	$\geq 5.0 \mu\text{m}$	$\geq 10 \mu\text{m}$
Class 1	3000	N/A	0	0
Class 2	300,000	N/A	2000	3
Class 3	N/A	1,000,000	20,000	4000



**Table 3** *Environmental standards (approximate comparisons)*

Federal Standard 209	Class:	100	10,000	100,000
Federal Standard 209E	Class:	M 3.5	M.5.5	M.6.5
British Standard 5295 (1976)	Class:	1	2	3
Pharmaceutical Inspection Convention (1981)	Grade:	A/B	C	D
UK "Orange Guide"	Grade:	1(A/B)	2	3
EC Guide (1989/1992)	Grade:	A/B	C	D
British Standard 5295 (1989)	Class:	E/F	J	K

### 31.3 CLEAN ROOM STANDARDS AND GMP GUIDELINES

The US CGMPs for finished pharmaceuticals<sup>7</sup> make no mention of clean rooms, in the specific sense, and offer no quantitative standards, for neither viable nor non-viable particles.

Sub-part C (Buildings and Facilities) includes, under Section 211.42 (Design and construction features), the following:

*(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:*

*(10) Aseptic processing, which includes as appropriate:*

- (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;*
- (ii) Temperature and humidity controls;*
- (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;*
- (iv) A system for monitoring environmental conditions;*
- (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;*
- (vi) A system for maintaining any equipment used to control the aseptic conditions.*

Sub-part C (Buildings and Facilities) adds, under Section 211.46 (Ventilation, air filtration, air heating and cooling), the following:

- (a) Adequate ventilation shall be provided.*
- (b) Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be used when appropriate . . .*
- (c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas.*

The FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing" (FDA, 1987)<sup>8</sup> is somewhat more specific. It does not refer to "Clean Rooms" as such, but it does draw a distinction between a "Critical Area, . . . in which the sterilised dosage form, containers and closures are exposed to the environment", and a "Controlled Area, where unsterilised product, in-process materials, and container/closures are prepared".

According to this FDA guideline, air in a critical area, "in the immediate proximity of exposed sterilised containers/closures and filling/closing operations is of acceptable quality when it has a per-cubic-foot particle count of no more than 100 in a size range of 0.5  $\mu$ m and larger (class 100) when measured not more than one foot away from the work site, and upstream of the air flow . . .". In a critical area the air "should also be of a high microbial quality. A incidence of no more than one colony forming unit per 10 cubic feet is considered as attainable and desirable".

This FDA guideline considers that, in a controlled area, the air "is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100,000 in a size range



of 0.5  $\mu\text{m}$  and larger (class 100,000) when measured in the vicinity of the exposed articles during periods of activity. With regard to microbial quality, an incidence of no more than 25 colony-forming units per 10 cubic feet is acceptable". (At the time of writing it is understood that a revised version of this FDA guideline is in an advanced stage of preparation.)

The 3rd edition of the UK GMP Guide (1983) set out, probably for the first time in any official GMP guideline, its own "Basic Environmental Standards for the Manufacture of Sterile Products". These were based on the British Standard 5295 (1976), but with the addition of a series of maximum permitted levels of viable organisms per cubic metre of air.

These standards were summarised in a table, which in addition to giving levels for particles generally, which are similar to those of BS 5295 (1976), also gave figures for

- Air-filter efficiency
- Air changes (per hour) in the room
- Viable organisms per cubic metre

There is also a cross reference to other classifications, including BS 5295 and US Federal 209 and a note that air pressures should "always be highest in the area of greatest risk", and that "air pressure differentials between rooms of successively higher to lower risk should be at least 1.5 mm (0.06 inch) water gauge" (*i.e.* approximately equivalent to a 15 Pa air pressure differential). This exemplified the concept of the air pressure "cascade".

The European Community GMP Guidelines (1989/92) refer to *Grades A, B, C and D*, and defined these in tabular "Air classification system for the manufacture of sterile products", as shown in Table 4.

In 1996, a revised version of Annex 1 ("Manufacture of Sterile Medicinal Products") to the EC GMP Guide was issued, which some have felt serves rather to cloud the issue than to clarify it.

This revised EC Annex offers a new tabular classification for environmental particle levels (see Table 5). It is noteworthy that this table differs from its British and EC antecedents in, as it were, "divorcing" inanimate particulate requirements from microbial limits. Hitherto, for example, "Grade B" meant, in one cubic metre of air, no more than 3500 particles at the 0.5  $\mu\text{m}$  level, none at 5  $\mu\text{m}$  and no more than 5 microorganisms, and so on. Now in this 1996 classification, a given Grade (A, B, C or D) refers *only* to the permitted inanimate particle levels. Furthermore, two sets of figures (different except, obviously, for Grade A) are given. One for the "at rest" state and one for the "in operation" state (see Table 5).

Textual comment, printed in this annex in relation to this table, reads as follows:

*"For the manufacture of sterile medicinal products normally 4 grades can be distinguished.  
Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a*

**Table 4** *EC GMP Guide (1992) air quality standards*

Grade	Maximum permitted number of particles per cubic metre		Maximum permitted number of viable microorganisms per cubic metre
	$\geq 0.5 \mu\text{m}$		
A (LAF workstation)	3500	None	$< 1^a$
B	3500	None	$5^a$
C	350,000	2000	100
D	3,500,000	20,000	500

<sup>a</sup> Reliable when only a large number of air samples are taken.

**Table 5** Airborne particulate classification' EC GMP Guide, Annex 1 (revised 1996)

Grade	Maximum permitted number of particles per cubic metre			
	At rest (b)		In operation	
	$\geq 0.5 \mu\text{m}$	$\geq 5 \mu\text{m}$	$\geq 0.5 \mu\text{m}$	$\geq 5 \mu\text{m}$
A	3,500	0	3,500	0
B (a)	3,500	0	350,000	2,000
C (a)	350,000	2,000	3,500,000	20,000
D (a)	3,50,0000	20,000	Not defined (c)	Not defined(c)

*laminar airflow workstation. Laminar airflow systems should provide a homogenous air speed of 0.45 m/s  $\pm$  20% (guidance value) at the working position.*

*Grade B: In the case of aseptic preparation and filling, the background environment for Grade A zone.*

*Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.*

Notes appended to the table, and keyed to “(a)”, “(b)”, “(c)” and “(d)” as they appear in that table, read as follows:

*(a) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.*

*(b) The guidance given for the maximum permitted number of particles in the ‘at rest’ condition corresponds approximately to the US Federal Standard 209E and the ISO classifications as follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10,000, M5.5, ISO 7 and grade D with class 100,000, M6.5, ISO 8.*

*(c) The requirement and limit for this area will depend on the nature of the operations carried out.*

No mention is made of differential room air pressures and required air changes are not quantified.

Further, three tables are also provided in this EC Annex. Two give “examples of operations to be carried out in the various grades”, in relation to terminally sterilised products and aseptic preparation, respectively, and the third provides “Recommended limits for microbial monitoring” in the different grades of room.

The two given “examples of operations to be carried out in the various grades” are shown in Tables 6 and 7, and the third (“Recommended limits for microbiological monitoring . . .”) in Table 8.

There is no need to expatiate on the ambiguities and imprecisions represented by these tables. The reader will surely have noted them (for a cogent analysis of this revised EC Annex, see Walker<sup>9</sup>).

The textual matter relating to these tables, as reproduced in Tables 6 and 7 may provide some clarification. It reads

*“The particulate conditions given in the table for the “at rest” state should be achieved in the unmanned state after a short “clean-up” period of 15–20 minutes (guidance value) after completion of operations. The particulate conditions for grade A in operation given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to*

**Table 6** After EC Guide Annex 1, revised 1996

Grade	Examples of operations for terminally sterilised products
A	Filling of products when unusually at risk
C	Preparation of solutions when unusually at risk
D	Preparation of solutions and components for subsequent filling

**Table 7** After EC Guide, Annex 1, revised 1996

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

**Table 8** Recommended limits for monitoring of clean areas in operation (EC GMP Guide, Annex 1, revised 1996)

Grade	Air sample (cfu per m <sup>3</sup> )	Settle plates (diameter 90 mm) cfu per 4 h	Contact plates (diameter 55 mm) cfu per plate	Glove print, 5 fingers cfu per glove
A	> 1	> 1	> 1	> 1
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

*demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself”.*

Further comment on the application of the various grades appears in the sub-sections on “Terminally sterilised products” and on “Aseptic preparation” and thus

*“Terminally sterilised products: Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where there is unusual risk to the product because of microbial contamination, for example, because the product actively supports microbial growth or must be held for long periods before sterilisation or is necessarily processed not mainly in closed vessels, preparation should be done in a grade C environment.*

*Filling of products for terminal sterilisation should be done in at least a grade C environment. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilisation.*

*Aseptic preparation: Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process, should be done in a grade A environment with grade B background.*

*Preparations of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered the preparation of materials and products should be done in a grade A environment with a grade B background.*

*Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.*

*Transfer of partially closed containers, as used in freeze drying should, prior to the completion of stoppering, be done either in a grade A environment, or in sealed transfer trays in a grade B environment.*

*Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered”.*

There remains to be considered the revised EC Guide Annex view of what we have termed the “divorced” environmental microbial standards. Paragraph 5 of the revised Annex reads, *inter alia*

*“5. In order to control the microbiological cleanliness of the various grades in operation, the areas should be monitored. Recommended limits for microbiological monitoring of clean areas in operation ... are ...”.* (see Table 8)

### 31.3.1 The Sterile Products Manufacturing Area or “Suite”

It cannot be repeated too often that great care must be taken to protect the product from contamination *throughout the entire manufacturing process*, and that it is not sufficient merely to rely on a final filtration and/or sterilisation to “clean things up”. It certainly *cannot* be hoped that if it fails to do so, then end-product testing, particularly by the notably fallible sterility test, will detect any problems. Thus, sterile products are manufactured in specially designed sterile manufacturing areas, or “Suites” of one or more clean rooms.

Within a sterile products suite, the various different manufacturing operations must be performed in a clean room (or rooms) appropriate to a particular operation. An air pressure “cascade” should be in operation, such that the air pressure is highest in the zone of potentially greatest risk (*e.g.* where exposed product is aseptically handled) and is progressively lower in areas of lesser risk. The entire suite should be at a higher air pressure than the general factory environment and/or “the outside world”.

### 31.3.2 Air Supply

The air supplied to various rooms must be of quantitatively specified quality. Air from the outside world, or from the rest of the factory, is neither suitable nor acceptable. Hence, no windows (or certainly no *openable* windows) to the outside are permissible. It follows that the air to the various rooms must be a forced supply, delivered via ventilation trunking, through filters designed and tested to ensure that air that has passed through them is of the required quality (that is, contains no more than the specified number of particles, and organisms, per cubic foot or cubic metre).

While it is common for coarser pre-filters to be used, in order to reduce the clogging of the final filters, it is important that the final air filters should be fitted at, or as close as possible to, the point of entry of the air into a room. This is usually at various places in the ceiling. It is also usual to design clean rooms so that it is possible to change these filters, as and when necessary, without having to do so from within the room itself (that is, for example, by making the change from above a “false” or suspended ceiling). This is to avoid contaminating the room with particles from the “dirty” side of the filter and to avoid no more personnel than absolutely necessary from having to enter the room.

It is generally considered that there should be a pressure differential between rooms of successively higher to lower risk of at least 15 Pa (approximately 1.5 mm water gauge = 0.06 in. water gauge), although some authorities (see, *e.g.* BS 5295) consider that a pressure differential of 10 Pa between a one classified area and another adjacent one of lower classification is acceptable, provided that the differential between the classified areas and adjacent unclassified areas is at least 15 Pa. Thus, the air pressure in the aseptic fill room should be higher than in solution preparation, and the pressure in both should be higher than in the changing rooms, which should in turn be at least 15 Pa higher than in the general unclassified area.

Pressure sensing devices (water gauges, manometers) must be installed to show the pressure differentials between rooms, and there should be audible or visible warning systems which sound, or display, alarm signals if the air supply fails and the required pressure drops.

Designing and installing air-supply systems is a highly specialised business, as is the balancing of air pressures so as to achieve the correct differentials and flows. Most usually clean rooms are constructed and installed, under contract, by specialists in this field. Careful selection of an appropriate specialist is crucial to success. Just as important is a clear, precise definition of just exactly what is wanted, and close and careful monitoring of the project, as the contract proceeds. When the installation has been completed and commissioned, it should be “handed-over”, complete with a certificate of conformity to specification. This should contain certification of at least.

- (i) Air-filter integrity – all air-inlet filters tested to confirm filter and seal integrity, and conformity to the specified standard.
- (ii) Air velocity – measured by anemometer to determine air velocity ( $\text{m s}^{-1}$ ) at the internal filter face of each air inlet.
- (iii) Air change rate – calculated for each clean room from the air velocity and the internal volume of the room.
- (iv) Air particle counts – as measured in each clean room, in terms of the number of particles (of specified size) per cubic metre, or cubic foot, at the positions and heights specified in the standard against which the clean rooms were constructed and commissioned.

With, in addition, reports of checks on airflow patterns, room-pressure differentials, lighting levels, heating and humidity.

Once the system has been installed and the suite is operational, it is necessary to continue to check and monitor air-filter (and seal) integrity and efficiency and that the air pressures and flows remain as required and as specified. It is also necessary to check airflow rates at filter faces and room air change rates (which should be at least 20 air changes per hour).

There will, of course, be people working in these clean rooms. There therefore needs to be heating or cooling of all this high-quality air to ensure the right level of comfort, particularly for operators clothed in the special clean room garments, which can make them uncomfortably hot. It is important that operators do not get too warm, since the more they sweat, the more particles and organisms they will shed.

The quality of the air, and surfaces, within the rooms must also be regularly monitored.

*Total particles* per unit volume of air may be determined by drawing a sample of air (of known volume) through a gridded filter membrane (capable of retaining particles of at least the size under investigation, *e.g.* of at least  $0.5 \mu\text{m}$ ), and then examining the membrane under a microscope for the size and numbers of particles. This is the reference method for demonstrating compliance with BS 5295. However, more often used are the various commercial brands of optical or laser particle counters.

*Microbial levels* (air-borne or on surfaces) in a clean room may be determined by use of:

- Settle plates
- Air samplers

- Surface sampling
- “Finger dabs”.

*Settle plates* are petri dishes containing sterile nutrient agar. The plates are most usually 90 mm in diameter (surface area approximately 0.006 m<sup>2</sup>), although plates of 140 mm diameter (approximately 0.015 m<sup>2</sup> surface area) have been used. It is thus necessary when reporting settle-plate results (and when establishing standards for settle-plate counts) to state both the size of the plate (s) and the time of exposure. For valid comparisons to be made between results obtained using different plate sizes, the results should be expressed as cfus 100 cm<sup>-2</sup> h<sup>-1</sup>.

It has been argued that settle plates do not give a measure of the concentration of micro-organisms in the air of a room. This is true, but it may equally be argued that, in providing a direct measure of the organisms which are depositing from the air and on to surfaces (or into containers), they do provide an indication of what the sterile product manufacturer really requires to know – the likely microbial contamination entering into, or onto, products (see Whyte<sup>10</sup>).

*Air samplers* are commercially available in a number of different types: cascade samplers, slit-to-agar samplers, single-sieve-to-agar samplers, centrifugal samplers, filtration samplers and liquid impingement samplers. In all these air sampling methods, knowledge of the sampling rate, the time period over which the sample was taken, and of the number of cfus counted after incubation will enable the determination of the number of viable organisms present in unit volume of air in the room.

### 31.3.3 Surface Sampling

Surfaces of walls, floors, work and equipment surfaces can be sampled using moistened sterile cotton swabs, which are then “streaked-out” on an agar plate, which is then incubated. Alternatively, and more conveniently except for less-accessible surfaces, contact (or “Rodac”) plates can be pressed lightly onto flat surfaces and incubated. Following the application of a swab, or a contact plate, the relevant surface area should be wiped with a disinfectant wipe.

### 31.3.4 Finger Dabs

Although “finger dabs” do not directly measure the microbial contamination of the air in a clean room, they do give an indication of the contamination picked up by operators from surfaces in the room.

After, or as, they leave the room, operators touch the tips of all digits of both gloved hands onto an agar plate, which is then incubated. (It should go without saying that the gloves should be discarded and fresh ones put on before an operator continues to work.)

A similar technique can be employed as a training exercise, outside the sterile area, by applying operators’ ungloved fingers (and indeed noses, ears or whatever) to an agar plate to provide them with a graphic illustration of the organisms present on the human body surface.

### 31.3.5 Frequency of Monitoring/Checking of Clean Room Parameters

#### 31.3.5.1 Physical.

- (i) Room pressure differentials – There should be a continuous automatic manometric measurement linked to unmistakable visual and/or audible warning signals that are triggered whenever pressure drops below the specified level. The manometer gauges should also be visually checked hourly, and the reading recorded at least once per day (or per shift). It is essential that the manometers are regularly calibrated.
- (ii) Air velocity and room air change rates – performed and recorded every 6 months.



- (iii) Air particle counts – performed daily (or batchwise) in the more critical areas, and weekly in the less.
- (iv) Air filter integrity and efficiency test – carried out once or twice a year, unless results of in-process physical and microbial monitoring indicate a more urgent need.

Airflow directions and patterns should also be occasionally checked, as convenient.

**31.3.5.2 Microbial.** While there is something like general agreement on the frequency of monitoring of physical clean room parameters (for example, frequency rates similar to those set out above are to be found in BS 5295), no such official or general agreement exists with regard to frequency of microbial monitoring. In these circumstances, the following seems to be a reasonable schedule for the different levels of clean room:

- At contained workstations (A) – daily or batchwise
- In clean rooms grade B/Cl.100 – daily
- In clean rooms grade C/Cl.10 000 – weekly
- In clean rooms grade D/Cl. 100 000 – weekly, without all aspects of microbial monitoring necessarily being carried out on each occasion.

(For more detailed information the reader is referred to the Technical Monograph No. 2 of the Parenteral Society, 1989.<sup>11</sup>)

## 31.4 THE STERILE MANUFACTURING AREA – CONSTRUCTION AND FINISHES

The surfaces of all floors, walls and ceilings should be hard, smooth, impervious and unbroken (*i.e.* no cracks, holes or other damage). There are three good reasons for this:

- (i) To prevent the shedding of particles from damaged or poorly finished brick, building block, plaster, *etc.*
- (ii) To prevent the accumulation of dust, dirt and microorganisms on, or in, rough or broken surfaces.
- (iii) To permit easy and repeated cleaning and disinfection.

Various materials have been used for floors, including welded sheet vinyl, terrazzo and various “poured” resin floors. A variety of basic structural materials are used for walls – bricks, blocks, plastic-coated metal panels and glass-reinforced plastics. All are acceptable, provided that the final finish provides a *smooth, impervious, unbroken* surface. Thus if a wall is constructed of brick or structural block, it must be smooth plastered and then coated with a hard-setting finish (polyurethane, epoxy, *etc.*), sprayed or painted on.

Welded sheet vinyl is also used as a wall finish, often as a continuation of the same material when it has also been used as a floor surface.

Where windows are installed, they should not be openable. They should be flush fitted on the controlled (or classified) area side. Where windows are fitted in a dividing wall between two classified areas or rooms, they should be double glazed so as to present a flush, ledge-less fit on both sides. If communication is necessary between adjacent clean rooms, this should be via “speech panels” (polymeric membranes that transmit sound while maintaining an airtight seal). They can be used back-to-back in double glazed windows. When installed in the more critical clean rooms, the usual protective grilles should be removed, as they are difficult to clean. Telephone and intercom installations should generally be avoided, certainly in aseptic processing rooms. If they are deemed



essential, in for example a solution preparation room, they should be purpose designed, flush mounted and with easily wipeable touch-sensitive controls.

Ceilings in sterile areas are often “false” or suspended to allow for the installation of air-supply ducting, and other services, above. It is important that any suspended ceiling is effectively sealed from the room below to prevent any possible contamination from the space between the false and the “real” ceiling.

Where floors meet walls and walls meet ceilings, the joins should be covered so as to avoid sharp corners that are difficult to clean, and it can harbour dust, dirt and microorganisms. It is also important that any such coving should be flush to both floor and wall (or wall and ceiling).

### 31.5 PERSONNEL

Even more than in relation to other types of manufacture, the *people* involved are the most important single factor. The person, or persons, who manage sterile products departments should have a full understanding of, and experience in, the special techniques, technologies and disciplines required – and of the underlying physical, chemical, microbiological and clinical reasons. They should be able to impart their knowledge and understanding to their staff, who should also be selected with care. Workers in sterile products areas should be mature (and that does not necessarily mean old) intelligent people who can fully understand not just what they have to do, but also the reasons for doing it. They must have innately high standards of personal hygiene and be readily able to conform to the special disciplines involved. They should also be free from any disease or condition that could represent an abnormal microbiological hazard to the clean room environment, and hence to the product. These conditions include, in addition to chronic gastrointestinal and respiratory tract diseases, short-term conditions such as colds, acute diarrhoea, skin rashes, boils, open superficial injuries and peeling sunburn. Operators should be required to report any such conditions, and supervisory staff should be on the look-out for them. There should be periodic health checks.

In addition to those who have chronic skin, respiratory or gut diseases, persons who have allergies to the synthetic fabrics used in clean room clothing, are abnormally high shedders of skin flakes or dandruff, have nervous conditions resulting in excessive itching, scratching, *etc.* or suffer from any degree of claustrophobia, are really not fitted to work in clean rooms.

No person who reports that they have a condition that would preclude their working in a clean area should suffer any penalty for doing so. The thought of loss of earnings might well persuade even the most virtuous worker to keep quiet about an adverse health condition.

A certain calm resoluteness of character is also most desirable. To be alone, or perhaps be just one of two or three in a clean room, in a full sterile suit with gloves, hood, mask and possibly goggles can prove a lonely, depressing, demotivating experience for some temperaments. Conversely, while a cheery, fun-loving, whistle-as-you-work attitude may well be salutary in some areas of human activity, it is entirely inappropriate in a clean room.

To minimise the contamination inevitably caused by the presence of people, the numbers entering and working in clean rooms should be kept to the minimum necessary for effective working. All activities, such as in-process testing and control, visual inspection and the like, which do not need to be conducted in clean room should be performed outside it.

All personnel, and that includes cleaning staff and maintenance engineers, required to work in, or otherwise enter a clean area should be trained in the techniques and disciplines relevant to the safe and effective manufacture of sterile products. This training, which should not be a “one-off” exercise but should be regularly reinforced with refresher training, should include the coverage of personal hygiene, the essential elements of microbiology and the purpose and correct wearing of protective clothing. Operators should be taught to “know the enemy”, and practical

demonstrations of growing cultures, finger dabs and the like will help to get the message home. Training should also include a strong motivational element, stressing responsibilities to patients' health and life, which are quite literally "in your hands".

Any outside persons such as building or maintenance contractors, who have not received the training and who need to enter clean areas, should only do so under close supervision and when wearing protective clothing appropriate to the area.

### 31.5.1 Personnel – Changing and Clothing

Personnel should only enter a clean area *via* changing rooms, where washing and changing should proceed in strict accordance with a written procedure. The operators should have been trained to follow this procedure, and a copy of it clearly displayed on the changing room wall. The procedure should be designed to minimise contamination of the protective clothing through, for example, contact with the floor on the "dirtier side" or with operators' shoes. Outdoor clothing should not be taken into clean room changing rooms. The assumption should be that outdoor garments have already been removed elsewhere, and that personnel are already clad in the standard "general factory" protective clothing. Wristwatches and jewelry should be removed as part of the changing process. Plain, simple wedding rings are generally considered to be an exception that is reasonable, sympathetic as well as expedient as many people find it impossible (physically or emotionally) to remove their wedding rings. However, the FDA are said not to agree on this point. Cosmetics, other than perhaps simple particle-free non-shedding creams, should not be worn.

The protective garments, which should include head and footwear, should be made from textiles specially manufactured so as to shed virtually no fibres or particles, and to retain any particles shed by a human body within. They should be comfortable to wear and loose-fitting to reduce abrasion. Fabric edges should be sealed and seams all enveloping. Unnecessary tucks and belts should be avoided, and there should be no external pockets. The garments should be worn only in the clean areas. A fresh set of clean (and if necessary sterilised) protective garments should be provided each time a person enters or re-enters a clean room. This should rigorously be enforced where aseptic processing is in operation. In other, less critical, clean rooms, it may be possible to relax this requirement and provide fresh garments once per day, if this can be justified on the basis of monitoring results and other control measures. Even so, fresh headwear, footwear and gloves should be provided for each working session.

Protective clothing, following use, should be washed or cleaned (and as necessary sterilised), and thereafter handled in such a way so as to prevent it from gathering contaminants and to minimise attrition of the fabric. It needs to be recognised that repeated wearing and laundering/cleaning (and sterilisation) can cumulatively damage the fabric so that it becomes no longer suitable for use. This is clearly something that needs to be monitored and controlled.

In grade C and D clean rooms one- or two-piece trouser suits should be worn, close fitting at the neck, wrists and ankles and with high necks. Hair, including any facial hair (beard or moustache), should be covered. Trouser bottoms should be tucked into overshoes or boots and sleeves into gloves.

In grade B clean rooms and/or when working at contained workstations, sterilised non-shedding cover-all trouser suits (preferably one piece) should be worn. Headwear should be of the helmet or cowl type and should totally enclose the hair and any beard/moustache. It should be completely tucked into the neck of the suit. Footwear should be of the boot or "boot-ee" type, totally enclosing the feet. Trouser bottoms should be completely tucked into the footwear. Powder-free rubber or plastic gloves should be worn with the garment sleeves neatly and completely tucked inside the gloves. Gloves should be regularly disinfected (*e.g.* with a sterile alcoholic spray or foam) during extended operations. Disposable face masks, covering both the nose and the mouth should be

worn. They should be discarded at least each time the wearers leave the clean room and whenever they become soggy. In the latter circumstances, it is of course necessary to leave the clean room to change the mask. Operators should be trained not to touch masks, or any other part of their face, with their hands when in a clean room.

Some authorities hold that, when working in an aseptic processing area, operators should wear close-fitting goggles. Indeed, the US FDA has been known to insist upon it. There are, however, those who would argue that any benefit, in terms of reduction in contamination hazard, is outweighed by the risks introduced by the additional operator discomfort and the misting of the goggle lenses.

When working at contained LAF workstations, operators should always work down-stream of the filter face and of any product, material or equipment that is being processed or manipulated at the work station. In other words, work should be conducted so that any operator-derived contamination is swept in a direction away from the work in hand. Hands or arms should not be interposed between the filter face and the product, as this would cause the air stream to sweep contamination from the operator onto the work – the very reverse of what is required.

There should be written instructions to operators on entering and working in clean rooms. These instructions should be used as a basis for training. They should also be prominently displayed in changing rooms. The following is intended to give an idea of the sort of thing that is necessary. It will also provide a summary of basic requirements for personnel in clean rooms.

### 31.6 INSTRUCTIONS TO OPERATORS ON ENTERING AND WORKING IN CLEAN ROOMS

- (i) Keep body, hair, face, hands and fingernails clean.
- (ii) Report any illnesses, cuts, grazes or respiratory, gut or skin problems.
- (iii) Follow the written changing and wash-up procedure *exactly*.
- (iv) Check that your protective clothing is worn properly.
- (v) Do not wear cosmetics, jewelry or wristwatches.
- (vi) Leave all personal items (wallets, coins, keys, watches, tissues, combs, *etc.*) in the changing room.
- (vii) Do not take papers, documents or paper materials into clean rooms, unless these have been specifically approved.
- (viii) *No* eating, chewing or drinking.
- (ix) Always move gently and steadily.
- (x) Do *not* move vigorously. *No* playing about, singing or whistling.
- (xi) Avoid talking unless absolutely necessary.
- (xii) Avoid coughing or sneezing. If these are unavoidable, leave the clean room.
- (xiii) Do not touch other operators.
- (xiv) Avoid scratching, touching nose and mouth and rubbing hands.
- (xv) Where gloves are worn, regularly disinfect them as instructed.
- (xvi) Always check for worn or damaged garments and torn gloves and change them as necessary.
- (xvii) Keep garments fully fastened up. Do not unfasten or loosen them.
- (xviii) Unless there is a special hazard involved, do not pick up dropped items from the floor.
- (xix) When working at a laminar flow workstation it is important to ensure that (1) nothing is placed between the air-filter face and the object, material or product that is being handled and that needs to be protected and (2) you always work down-stream from the air-filter face, and do not let your hands or arms come between the item that is being protected and the air-filter face.

## 31.7 CONTROL OF THE STERILISATION PROCESS

### 31.7.1 General

Whatever type of sterilisation process is employed, it must be one that has been properly *validated*. Although it can and indeed has been argued that the intrinsically sound concept of validation has been pushed by some “experts” and regulatory authorities to extremes that border on the ludicrous,<sup>12–14</sup> it cannot reasonably be questioned that thorough validation of the process used for sterilisation is a crucial issue in the manufacture of sterile products.

Particularly rigorous attention should be given to validation when the adopted sterilisation method is non-standard or employs a non-standard cycle (That is, it is not one that is set out and described in the Pharmacopoeias). Where possible, heat sterilisation is the method of choice.

Before any sterilisation process is adopted, its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated by physical measurements and by the use of biological indicators where appropriate. The process should be re-validated at scheduled intervals, at least annually, and whenever modifications have been made to, for example, process parameters or equipments.

It should be obvious, but in practice it has not always seemed so, that for effective sterilisation the whole of the material, or batch, must be subjected to the required treatment, and the process should be validated so as to demonstrate that this is achieved – each and every time. Thus, validated loading patterns should be established for all sterilisation processes that involve loading materials or products into a chamber or other form of steriliser. It is unreservedly insufficient merely to know that, say, in an autoclave, some part or parts of the load reach and hold the desired temperature for the specified time. The essential thing is that the coldest part of the coldest item in the coldest part of the load reaches the required temperature and holds it for the required time. If the achievement of those conditions entails other parts of the load reaching temperatures well in excess of those required for sterilisation, the design of the process and/or of the autoclave must seriously be called into question.

Biological and other indicators should be considered only as an additional method for monitoring a sterilisation process. They may be taken as an indication that a process may have failed, but because of their inherent variability they cannot, alone, be regarded as an indication that it has succeeded. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

There should be a clear means of differentiating products that have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process. Again, they cannot be taken to give a reliable indication that lot is, in fact, sterile.

The “raw” sterilisation records (*e.g.* time/temperature charts) of each sterilisation run should be retained as part of the batch-manufacturing record. They should be reviewed, along with the other batch documentation, as part of the batch-release procedure.

### 31.7.2 Sterilisation by Heat

Each heat-sterilisation cycle should be recorded on a time/temperature chart on a suitably large scale or by other appropriate equipment with suitable accuracy and precision, for example a digital printout device. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position. Where control of the cycle is automatic, the heat-sensing *control* probe should be independent of the *recorder* probe. (If the same

probe was used for both purposes and it was defective, it could actuate an inadequate cycle, yet still signal an apparently satisfactory one.)

Chemical or biological indicators may also be used, but should not take the place of physical measurements.

Care needs to be taken to guard against re-contamination of a sterilised load during the cooling phase. Any cooling fluid in contact with the product should have been sterilised, unless it can be infallibly shown that any leaking container would not be released for distribution. Air admitted before the chamber doors are opened should be filtered, and water used for spray cooling should be water for injection quality.

### 31.7.3 Steam Sterilisation

It is important to ensure that the steam used is of a suitable quality ("clean steam") and does not contain additives, or other substances, which could cause chemical contamination of the product, material or equipment being sterilised.

Both temperature and pressure should be used to monitor the process. Where automated control and monitoring systems are used for these applications, they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading from an independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. When a vacuum phase is part of the cycle, frequent leak tests should form part of the routine maintenance programme for the chamber used.

Items to be sterilised, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but that prevents re-contamination after sterilisation.

### 31.7.4 Dry Heat

It is important that there should be adequate air circulation within the chamber and a positive air pressure must be maintained to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

### 31.7.5 Ethylene Oxide Sterilisation

In sterilisation, direct contact between the gas and the microbial cells is essential for effective sterilisation. Organisms occluded in crystals, or coated with other materials, such as dried protein, may well not be killed. The nature and quantity of any packaging material can also markedly affect the efficacy of the process. Before exposure to the gas, the materials should be brought into equilibrium with the required temperature and humidity. Throughout the cycle, records should be made of the cycle time, temperature, pressure, humidity, gas concentration and total amount of gas used. These records should form part of the batch record, and used in the final evaluation of the batch for release/reject. Ethylene oxide sterilisation is an instance where use of biological indicators should be considered mandatory, rather than merely a possible useful adjunct. The generally recommended organism is *Bacillus subtilis* var. *niger*, deposited on a suitable carrier. The positioning of these indicators should be selected following validation studies to determine those parts of the load that are most difficult to sterilise. The information derived from the use of these biological indicators should form part of the batch-manufacturing record, as evaluated when making the final release/reject decision. After sterilisation, the load must be held, in a manner, which will prevent recontamination under ventilated conditions to allow "degassing" of residual gas and reaction products.

### 31.7.6 Radiation Sterilisation

During gamma irradiation sterilisation, the dose received should be monitored throughout the process by the use of plastic dosimeters inserted in the load in sufficient numbers, in packs sufficiently close together so as to ensure that in a continuous process there are always at least two dosimeters in the load exposed to the source. The standard red perspex dosimeters, as for example prepared by the UK Atomic Energy Authority at Harwell, give a reproducible, quantitative, dose-related change in absorbance, which should be read as soon as possible after exposure to the radiation. Electron beam sterilisation is rather more difficult to control. The dosimeters used are usually in the form of PVC films. In both cases, the dosimetry results should form part of the batch record. Biological indicators can be used, but *not* as a proof of sterilisation. Radiation-sensitive adhesive coloured discs are used, but only (repeat, *only*) as a means of indicating that a package has been exposed to radiation and not as a proof of sterilisation.

### 31.7.7 Filtration Sterilisation

In filtration sterilisation, which should only be used when it not possible or practicable to sterilise by other more secure means, non-fibre shedding filters, which are demonstrably capable of removing microorganisms, without removing ingredients from the solution or releasing substances into it, must be used. It is often advisable to use a (possibly coarser grade) pre-filter to first remove larger particles and thus reduce the load on the sterilising filter. Because of the potential additional risk of filtration as compared with other sterilisation methods, it is considered by many to be a sound practice to follow the first sterilisation grade filter with a second, in series, down-stream. The integrity of the sterilising (and sterilised) filter assembly, *in situ* (not just the filter in isolation), should be confirmed before use, and re-checked after use by such methods as the so-called bubble-point, pressure-hold or forward-flow tests. The time during which a sterile-filtered bulk solution is held, pending filling and sealing in its final container should be kept to a defined minimum, appropriate to the conditions under which the bulk-filtered solution is stored. Any one filter should not normally be used for more than one working day, unless a longer period of use can be justified by sound validation studies.

### 31.7.8 After Sterilisation

Of major importance is the need to avoid re-contamination of a sterilised product or material, and the mixup of sterilised with non-sterilised items. Ethylene oxide sterilisation is a special case where it is necessary to hold sterilised material under controlled ventilated conditions to allow any residual ethylene oxide and its reaction products to diffuse away. This presents additional problems in the prevention of re-contamination and mixup.

Besides the chemical analytical testing to confirm compliance with specification, sterile products also require to be subjected to further testing that is specific to this type of product. This includes

- Examination for particles
- Sterility testing
- Leak-detection testing, and possibly
- Pyrogen (or endotoxin) testing.

### 31.7.9 Examination for Particulate Contamination

The EC GMP Guide's revised (1996) Annex 1 – "Manufacture of Sterile Medicinal Products" requires that "Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects", and adds that when this is a visual inspection



“it should be done under suitable and controlled conditions of illumination and background”. It adds that operators engaged in this work should pass regular eyesight tests, with spectacles if normally worn, and be given frequent breaks from inspection. Pharmacopoeias (*e.g.* British, European and United States) have also variously set down requirements for the examination of filled parenterals for visible and sub-visible particles.

Visual inspection is a fallible process, relying as it must on subjective, hardly quantifiable judgments under conditions, which are difficult to standardise. Not only is it of doubtful value, it is also a dreary, time-consuming job that most workers would wish to avoid. It is not surprising, therefore, that various automated electronic methods have been developed. For a comparative review of the techniques and equipment available see Akers (1985).<sup>15</sup>

### 31.7.10 Sterility Testing

The severe statistical limitations of the compendial sterility test are generally acknowledged. There are also microbiological limitations, in particular the fact that there is no “universal” growth medium upon or in which all forms of microorganisms may be expected to grow. As generally practiced, sterility tests will not detect viruses, protozoa, exacting parasitic bacteria or many thermophilic and psychophilic bacteria. Furthermore, organisms, which have been damaged but not killed by exposure to sub-lethal levels of “sterilisation”, may not show up in the standard sterility test as they may require conditions for growth in terms of nutrients, temperature and time that the test does not provide.

Despite these acknowledged limitations, the test continues to be performed even by those who would accept that it has little real significance in terms of the quality of the product. This would appear to be due largely to regulatory requirements, and to a nervous perception of potential legal implications. The GMP guidelines appear to accept the limitations by declaring, for example, that “The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured”. The EC “Sterile Annex” (rev. 1996) considers that samples taken for sterility testing should be “representative of the whole batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination”. Examples given are of (a) samples taken from the beginning and the end of an aseptic run and “after any significant intervention” and (b) samples from the “potentially coolest part of the load” in a heat sterilisation.

There will be those who would consider that it would be difficult to encompass these requirements, within the limitations of the twenty unit sample that is usually taken, and they would be right. Akers<sup>15</sup> has considered alternative statistical sampling methods.

### 31.7.11 Leaks and Leak Testing

The Parenteral Society’s Technical Monograph No. 3, “The prevention and detection of leaks in ampoules, vials and other parenteral containers”<sup>16</sup> rightly lays stress on the primary importance of *preventing* the formation of leaks.

The two main causes of leaks in ampoules are cracks in the glass and faulty sealing. Mechanical cracks can be caused by collision or abrasion of ampoules, one with another, or with or against other objects, during or after filling. In addition, thermal cracks can be caused in the glass through rapid cooling from higher temperatures, for example by contact of hot glass with cold machine parts. Such thermal cracks may develop immediately, or regions of stress may be induced, which develop into cracks later. Crack-inducing stresses can be caused during the original ampoule-forming operation, or during sterile product manufacturer, during heat sealing, ceramic printing and heat sterilisation. Faulty ampoule seals can arise from maladjustment or faulty setting of ampoule filling and sealing machines.



Methods aiding prevention are obvious: at all stages from the original forming of the ampoules to the dispatch of the finished product, careful steps should be taken to prevent impact and attrition of glass against glass, or with or against any other objects. Empty and filled ampoules awaiting further processing should be assembled neatly on their bases, and not just loaded haphazardly in basket loads. To prevent thermal stress cracks, contact must be avoided between hot glass and cold metal. Careful attention is necessary to machine adjustment, including flame settings, to avoid faulty sealing. With proper setting, draw sealing is less likely to give rise to faulty seals than tip sealing.

There are a number of “traditional” methods for leak-testing ampoules. They include various pressure/vacuum tests such as the common dye intrusion (or “Dye Bath”) test, liquid loss and “Blotting paper” tests. These, and other techniques have been (and are) used, and they all have their limitations, even hazards – for example is that of dye solution entering an ampoule through a leak and then escaping subsequent detection.

Although not entirely free of problems and limitations, automated high voltage detection methods are more sensitive, and are not subject to the limitation of “traditional” method such as fallibility of human inspectors and hazards of undetected dye intrusion. They also have the further advantage that they can detect points of weakness, such as areas of thin glass, which at the time of testing are potential, if not actual, leaks.

With glass vials, the major stress should, again be upon prevention and not merely detection of leaks. Measures to prevent mechanical and thermal stresses and cracks are the same as that for ampoules. To minimise leaks arising from dimensional, physical and chemical inadequacies or incompatibilities, it is crucial that detailed and comprehensive specifications are agreed with suppliers of both vials and closures, and that compliance with specification is checked on all incoming deliveries.

In contrast with a fairly general acceptance of the need for 100% leak testing of glass ampoule products, a brief survey carried out in 1991/1992 indicated that 100% leak testing of glass vial products was the exception, rather than the rule. This is clearly unsatisfactory from a patient safety point of view, unless it can be shown that there is little if any possibility of leaks in filled and sealed glass vials, which does not appear to be the case. Pressure/vacuum tests can be applied to glass vial products, with the same limitations and problems for ampoules. However, based on the experience of the relatively few manufacturers of glass vial products that have tried the technique, it seems that automated high voltage detection is applicable to glass vial products. Such trials that have been conducted have shown that leaks do occur in production batches of filled glass vials, both in the vial body and in the closure system.

Leaks in LVP plastic containers can be caused by

- faults in the welding or sealing of the container when it is fabricated from the plastic sheets,
- inadequate “fit”, or sealing, of components (tubes, closures, ports) attached to the bag,
- mechanical damage caused by contact with sharp or abrasive surfaces during filling, sterilisation and subsequent handling and
- pinholes or splits occurring during bag printing.

Pre-filled syringes and cartridges would clearly seem to represent a serious patient hazard if they have leaks. Somewhat disturbingly, however, it does appear that there is virtually no information available on the incidence and causes of leaks, nor on suitable methods of leak detection.

### **31.7.12 Pyrogen, or Endotoxin, Testing**

The reaction in humans to injection of pyrogens can include chill, shivering, vasoconstriction, dilation of pupils, respiratory depression, hypertension, nausea and pains in joints and head, in addition to (or as a result of) the “fire”, or rapid increase in body temperature, which the term

suggests. It is reasonable to assume that a patient receiving an injection is, in most cases, already ill. This additional stress to the system cannot be considered as anything less than highly undesirable.

Some substances, including some active drug substances (or “APIs”, *e.g.* some steroids) and some viruses are pyrogenic *per se*, but in terms of sterile products manufacturing on an industrial scale, the most significant pyrogen is the bacterial endotoxin that is derived from the outer cell wall of certain Gram-negative bacteria. This substance is a complex, high molecular weight lipopolysaccharide, soluble in water and relatively heat stable. It can withstand autoclaving, and can pass through the 0.2 µm pores in the filters commonly used for sterilisation by filtration. Destruction, or removal, of microorganisms will not necessarily destroy pyrogenic endotoxin. There is thus another very good reason for keeping bacterial contamination at the lowest possible level at all stages in the manufacturing process, in addition to ensuring the lowest possible challenge to the sterilisation procedure. It is to reduce the chance of the presence of endotoxins. Prevention is, as ever, far better than later detection.

Pyrogenic contamination can arise at any stage in the manufacturing process. It may be present in starting materials, most notably in the water used to make solutions – hence the importance of good-quality water, produced by well-designed and monitored systems. It can be present on the surfaces of containers. It is unlikely to be present on glass containers, as manufactured, in view of the temperatures at which glass is blown or moulded, but it can be introduced by washing and rinsing glass containers with water that is not pyrogen free. It can be removed from glass containers by exposure to temperatures of 250°C or above, in for example a sterilising and de-pyrogenating tunnel. Once present in a solution, it is difficult if not impossible to remove. The answer is to not let it develop in the first place.

The traditional test for the detection of pyrogenic substances relies on the fact that the febrile response of rabbits resembles that of humans. The solution under test is injected into rabbits, and the rise, if any, in their rectal temperatures measured over the period of the test. The rabbit test has a number of disadvantages: it is a limit, rather than a quantitative test; it is time-consuming and subject to the variability and vagaries inherent in all biological test methods; and it cannot be used for solutions of substances that themselves prompt or inhibit a pyrogenic response.

A method that overcomes these problems, which can be used for quantitative determinations, and is more sensitive at low endotoxin levels is based on a discovery that a lysate of the amoebocytes from the blood of the so-called horseshoe crab (*Limulus polyphemus*, found mainly along the north-eastern seaboard of the American continent), in contact with bacterial endotoxin shows turbidity, or undergoes clotting (gelation). This is the *Limulus* amoebocyte lysate, or LAL, test. The LAL test kits are widely available from commercial suppliers. Although, at it is most simple, the turbidity/gelling end-point is determined visually and the method has been refined to permit more precise turbidimetric, colorimetric and nephelometric determinations (see Akers<sup>15</sup>).

### 31.7.13 Parametric Release

This concept, and its related terminology, emerged in the early- to mid-1980s and was originally related solely to the sterility (or otherwise) of terminally heat-sterilised products. That is, it did not originally bear upon other release criteria, or on the release of any other products, sterile or otherwise.

One of the first (if not *the* first) “official” publications on this subject is an FDA “Compliance Policy Guide” on “Parametric Release – Terminally Sterilised Drug Products”. This guide provides a definition as follows:

*“Parametric Release is defined as a sterility release procedure based upon effective control, monitoring and documentation of a validated sterilisation process cycle, in lieu of release based upon end-product sterility testing”.*

(Present writers emphasis)

Assuming the linguistic transplant “in lieu” means the same in United States as it does in Britain (and indeed in France) – then if “sterility release” may be based on “effective control . . .” *etc.*, in place of a sterility test result, then the inverse corollary is surely implied that if a sterility test *has* been passed, then “effective control, monitoring and documentation of validated sterilisation process” is not necessary. This is contrary to all the principles of quality assurance in the manufacture of sterile products, and is thus presumably not what the FDA really meant.

This FDA guideline then goes on to list the actions that must be taken (and documented) as pre-conditions for parametric release.

In brief, they are given as:

- (1) *Validation of the cycle to achieve a reduction of the known microbial bioburden to 10<sup>0</sup> (sic), with a minimum safety factor of an additional six logarithm reduction. (Validation studies to include heat distribution, heat penetration, bioburden, and cycle lethality studies.)*
- (2) *Validation of integrity of container/closure.*
- (3) *Pre-sterilisation bioburden testing on each lot, pre-sterilisation, and checking comparative resistance of any spore-formers found.*
- (4) *Inclusion of chemical or biological indicators in each truckload.*

Worthy though the intention undoubtedly is, it is difficult to refrain from asking the question: Is not this (with the possible exception of the inclusion of biological indicators in *every* load) a list of things that should be done anyway, whether the lot is to be sterility tested or not?

This statement on “parametric release” provides an indication of the type and range of process parameters, which need to be considered before a product may reasonably be released without testing the end product for a specific quality characteristic. In this particular instance, a notably unreliable test procedure (the sterility test) may be abandoned, with at least a theoretical possibility of regulatory approval, in favour of a rigorous concentration of effort on actions that will provide a significantly higher level of assurance of sterility – an excellent notion in this context, and one that has been adopted (with official approval) by a few sterile products manufacturers. But they *are* surprisingly few. The reason for this probably lies in a not unfounded fear that, should action be taken for damages in the case of an alleged sterility failure, learned judges will probably consider “passed pharmacopoeial sterility test” – a better defence than technical and statistical arguments that they will not understand.

Recently, the European Commission has issued a new “Annex 17 to the EU Guide to Good Manufacturing Practice”<sup>17</sup>, with a “proposed date for coming into operation” in January 2002.

Regrettably, as is so often the case with documents from this source, there is the usual poverty of linguistic expression and a liberal sprinkling of odd, ambiguous and paradoxical utterances. However, the oddest thing about this annex is its overall ambivalence. The standard form for documents of this type is that they are promulgated by regulatory bodies and directed at *manufacturers* as guidance on how to comply with GMP, both in general and in specific instances. This so-called Annex 17 reads rather more like a set of guidance notes for regulators considering whether or not to approve an application from a manufacturer to be permitted to release parametrically. As such, it would appear to have got lost and wandered into “Rules and Guidance for Pharmaceutical *Manufacturers* . . .” by mistake.

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## **Part 4: Support Services to GXPs**





# Statistics for QA Auditors of GLP and GCP Studies<sup>†</sup>

I. TOWNSHEND

## 32.1 INTRODUCTION

Sampling principles are applicable to many of the activities of Quality Assurance (QA) professionals. However, it is traditionally in the area of data auditing and particularly in auditing those data appearing in reports, that sampling is used, as mentioned in Chapters 10 and 11. Recourse to sampling is often induced by an imbalance in resource and the size of the task. This leads to the hope that a conclusion about data quality can be drawn without detailed examination of all the data. Reducing the auditor's task should improve performance, and keep 'auditor error' smaller than the error rate that is being measured.

Sampling can vary from 100 per cent to almost 0 per cent. The selection can also be random, systematic, or arbitrary, the last often being referred to as 'spot checking'. One approach may be used throughout, or several for different sections of the task.

This chapter will cover:

- (i) The choice of a sampling method for QA use.
- (ii) Quality standards.
- (iii) Practical approaches to auditing.
- (iv) Refinements to the sampling system.

Commonly used terms are defined in the glossary at the end of the book. This is not an exhaustive treatment of sampling, since whole books can be and have been written on the topic. Within a single chapter, only an introduction to some of the basic concepts can be given. The reader is referred to the bibliography for further information.

The chapter will not cover:

- (i) Details of particular sampling schemes.
- (ii) The mathematical basis of such schemes.

The author has used schemes based on British Standard (BS) 6000/6001 (1972) for several years, and would recommend it as a reasonable approach to report auditing.

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<sup>†</sup>This chapter was felt by the Editor to be of significant importance and taken from *Good Laboratory and Clinical Practices*, P.A. Carson and N.J. Dent (eds), Heinemann-Newnes, 1990.

## 32.2 CHOICE OF SAMPLING METHOD

### 32.2.1 Statistical Methods

The purpose of a QA audit of data is usually to determine whether (or not) a complete reported dataset conforms with the raw data according to standards set within the organization or by legislation. Methods based on the theory of probability allow confidence limits to be placed on the findings of the audit. Such approaches are often referred to as 'statistical methods'. By their means valid conclusions can be drawn about all the data, not just about the proportion checked.

### 32.2.2 Other Methods

In contrast, non-statistical methods provide a more limited basis for extrapolation. It places undue responsibility on the auditor, and provides no logical basis for acceptance or rejection of the whole dataset. However, in certain circumstances, as when a single automated transcription of data is being checked, it is possible that spot checking may yield useful results more economically than other methods. Nevertheless, in view of the risks, the results of an audit should never depend solely on such checks.

It therefore follows that if QA is to assess whether (or not) an individual dataset meets agreed quality criteria, then the method used must be based on either 100 per cent audit or statistical sampling. Recording the results of these two methods will allow the identification of any regular pattern, such as a historical trend, or periodic clusters of poor-quality documents, which will help study management to respond more effectively to audits.

A combination of 100 per cent audit and statistical sampling is often used to take account of the variation in logical weight attributed to different sections of the dataset.

## 32.3 STANDARDS

In order to assess whether a dataset as a whole complies with the standards of the organization, these standards need to be quantified, usually by defining an acceptable limit to non-conformity and some limit to the desired probability of detection. A typical statement might be: 'A dataset containing 2.5 per cent or less of non-conformities will stand a chance of 0.90 or more of being accepted'. This defines the limit of acceptable quality expected as a process average. It does not guarantee that all datasets will be better than the limit, since this could only be achieved with 100 per cent audits. It is worth taking time to agree such a limit for the organization as a whole.

The emphasis throughout this chapter is on sampling based on acceptable quality limits. However, schemes can be based on rejection of datasets which are worse than a 'limiting quality'.

### 32.3.1 Multiple Common Standards

It is likely that some sections of the dataset are considered to carry more logical weight than others; they are more important to the end use of the dataset. This is particularly likely where events are recorded and where presence or absence of a particular event is critical to the setting up or outcome of a study. Examples are death, heart attack, discovery of a tumour, *etc.* Such data, in which a single non-conformity might render the dataset unsuitable for its intended use, should be treated separately. An observed non-conformity will be referred back to the producer, and if no valid defence is cited, it will be classified as an error. Clearly, by definition, any level of error is unacceptable in this data. While no audit process can guarantee absolute accuracy in a dataset, it is usual with such critical data to rely on a 100 per cent audit.

Careful judgement is required when defining which data are critical and which are not. For example, in many trials clinical chemistry will be considered non-critical. In practical terms

increasing the proportion of data considered critical will absorb more of the resource available for auditing. It will also increase the risk of the auditor making an error, and in this way be counterproductive. The use of two standards for data is quite common and has several merits:

- (i) It allows audit resource to be concentrated on important sections of data.
- (ii) It gives extra protection against errors in critical data.
- (iii) It preserves the principle of drawing conclusions about the whole dataset from the findings in a sample of the data.

The concept of more than one category of data can be extended to multiple quality levels, for example critical data – zero errors acceptable, major data – 0.90 probability of acceptance if 2.5 per cent of non-conformities, minor data – 0.90 probability of acceptance if 10 per cent of non-conformities. For example, clinical data recorded by the physician might be considered major data, and data recorded by the patient might be considered minor data. There is no theoretical limit to the number of quality levels that may be employed.

However, complexity can be counterproductive, and many applications are successful with just two levels.

Standards of acceptability need to be agreed between the owners of the data and those who are to make use of it. Often these will be two departments within the organization, or, in the case of contracted studies, the sponsor and the contractor. The QA audit then provides a consistent measure of the ongoing quality of the data.

**32.3.1.1 Consequences of Raising and Lowering Acceptable Quality Limits.** Lowering the limit of acceptable quality, for example from 2.5 to 1 per cent, will have the desirable effect of improving the quality of the outgoing datasets. This will be perceived as a highly desirable change, and many arguments can be put forward in support of such a change, particularly in sensitive areas of research. It will appeal to facility management, since it will yield a better quality product. The cost of such a change made in isolation without any parallel change in report production procedure is inevitably an increase in the number of rejected reports, which will need to be managed. Productivity will fall as the number of reports requiring reworking increases, and this cost may well nullify the expected advantage from the initial change in acceptable quality limit.

Raising the limit of acceptable quality will permit some reports with more non-conformities to pass audit. In parallel it will reduce the number of failures. In practice the acceptable quality limit should not be altered in isolation. Consideration has to be given both to the capability of the report-production system and to the requirement of the end user. Both producers and users should discuss and agree with the standards used.

## 32.4 PRACTICAL APPROACHES TO AUDITING

Sampling procedures primarily assess the quality of individual datasets that are part of a series. Criteria for pass or fail are set tightly until some experience as to the performance of the production process has been built up. Setting tightened criteria is dealt with under 'Refinements of the basic system'. This section presents the procedure for a single dataset in a series.

### 32.4.1 Drawing the Sample

The sampling procedure is a critical part of the auditing process, so that the methods should be agreed in advance and be part of a standard approach. Within the standard procedure will come the method of drawing the sample and the criteria of acceptance. These could be based on BS 6000/6001 (1972) or an equivalent, such as American National Standard ANSI-Z1.4. While these

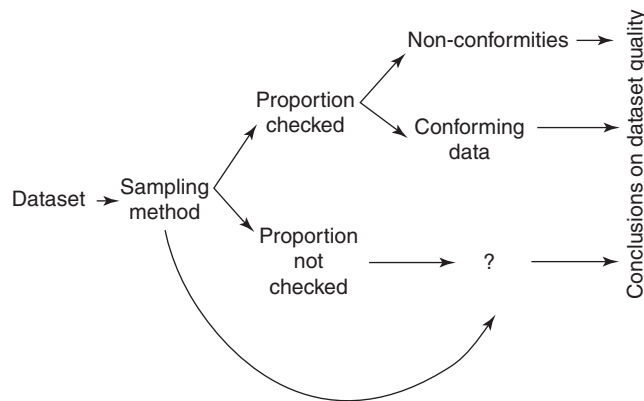
standards were originally produced for use by manufacturers, they can be adapted by the user for report auditing. The terminology used in report auditing differs from that in manufacturing, but equivalents can be defined. To draw the sample (Figure 1) it is necessary to know the number of the items in the dataset. While they are counted, they are identified by a suitable index (*e.g.* page, row and column). A microcomputer can ease this tabulating and counting of a dataset, and is useful in the actual drawing of the sample. At the same time the standard is consulted for a description of the appropriate sample. It will show whether (or not) sampling is possible for a dataset of this size (Figure 2) and will quote a sample size and an acceptable number.

There will also be information on the probability of acceptance of datasets of a particular quality. If these probabilities lie outside the limits agreed for the data audit, then there is no alternative but to conduct a 100 per cent audit. If they are equal to or better than the limits agreed within the organization, then the sampling can proceed.

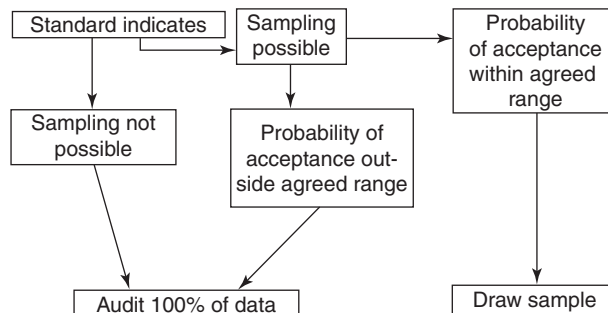
Random numbers between one and the total count of dataset items are then drawn using either tables or a computer generator. These are then applied to the dataset, using the index. The actual items within the dataset which are to be checked are marked.

### 32.4.2 Evaluating the Results of the Sampling

After the checking of the sample for non-conformities, they are counted and the total compared with the acceptance number given in the standard for the particular sample drawn.



**Figure 1** Drawing the sample



**Figure 2** Deciding whether sampling is possible

### 32.4.3 Failure

If the total number of non-conformities exceeds the acceptance number, then the dataset fails and should be returned to the producer for resolution. Opinions differ as to whether either the items checked or those checked and failed should be identified to the producer. Identifying them can give a false sense of security, since it might infer that attention to the identified non-conformities will automatically bring the dataset up to the required standard. This is not a valid conclusion. Use of statistical methods has the real benefit that the non-conformities identified probably indicate non-conformities throughout the whole dataset, not just in the sample. Correction of just the identified non-conformities and re-sampling will often produce another failure, though some improvement in quality is usually observed when this is done.

The first failure implies that the whole dataset should be reworked and that all non-conformities which are found should receive attention. Subsequent sampling and audit will then usually result in a pass.

It must also be recognized that there is a small but discrete probability that datasets with an acceptable quality will fail the sampling test. This probability is a direct consequence of any approach short of a 100 per cent sample, and this risk (usually less than 0.1) will be clearly quantified in the standard used.

### 32.4.4 Pass

If the total number of non-conformities is less than or equal to the acceptance number, then the dataset passes the test and is acceptable according to the agreed standards. Usually the sample will be observed to contain non-conformities. These should be drawn to the attention of the producer, and he should be given the option of ignoring or correcting them. Either approach is acceptable, but should be written into the agreed procedure.

Again it must be recognized that because of the method used there is a measurable probability that datasets with an unacceptable quality will pass the sampling test. This risk will be clearly quantified in the standard used.

### 32.4.5 False Passes and False Failures

Much emphasis has been placed on the possibility of false indications being given by the sampling tests. While these risks are real, they have to be seen in the context of the alternatives. One hundred per cent samples would give much higher degrees of precision, but would make probably unacceptable demands on the resources available. Such extensive auditing would also considerably increase the chance of auditor error, which would confound the inference being drawn from the audit. The other alternative (the ubiquitous 10 per cent selected by the auditor in a non-random manner) provides little inference at all as to the quality of the dataset as a whole, and only unreliable indications of the quality of the unaudited part of it.

Against these alternatives the small quantifiable risks of statistical samples are a major step forward. If a data audit is worth doing, then it should be capable of producing quantifiable results.

### 32.4.6 Non-Conformities Outside the Sample

While the conclusion of the sampling test must only be based on those items selected randomly, frequently non-conformities are observed elsewhere during the audit, perhaps in the same row or column of the dataset as the item sampled. These should not be ignored. As part of the established role of a QA professional, these should be drawn to the attention of the producer of the dataset.

### 32.4.7 The Value of Records

A record of the dataset audited, the sample drawn, the audit result, and the responses from the producer, should be kept as part of the quality history. This can then be referred to when an individual dataset fails the sampling test. Monitoring the sampling scheme and noting the quality achieved are of assistance to management both when quality is consistently above the required standard and when failures are revealed.

## 32.5 REFINEMENTS OF THE BASIC SYSTEM

### 32.5.1 Switching Rules

Statistical sampling schemes are mainly designed for control of production of a series of batches. In the context of dataset audits this is taken to be a series of datasets produced by the same process, that is the same group of people, machines and procedures.

The sampling schemes have facilities built in to allow the procedure to respond to the results of recent samples. This is an attempt to respond to any evidence of change in the quality of datasets being sampled. A continuous series of successful outcomes will indicate that datasets are probably being produced with quality well inside the acceptance quality limit (AQL) and, accordingly, the sampling can be relaxed. This will mean smaller samples, but the results are monitored closely to respond to any indication of a slide back towards the AQL.

One consequence of a series of failed batches is a tightening of the sample scheme, with larger samples being taken. If failures continue, sampling is suspended until the process is improved.

The methods of making changes in the sample in response to a perceived change in the quality of datasets is described in a series of switching rules, which control switching between sample levels. They drive both increases and decreases in the sample size. Thus the rules (particularly those for tightened inspection) encourage or even force improvement in the underlying process.

### 32.5.2 Skip-Lot Systems

The switching rules allow a stepwise relaxation of sampling in response to a series of datasets with observed quality better than the AQL. If the outcome of relaxed sampling is still a series of passes, then a logical extension of this reduction in sampling is to omit the checking of whole datasets. Clearly, this increases the risk of non-conformities remaining undetected. However, against a history of good performance this step may be justified. Its benefit is clearly to prevent having QA staff interminably auditing datasets which always pass the test. Selecting datasets at random according to a set of skip-lot rules uses the auditing resources efficiently and helps to prevent the boredom that might result in auditors overlooking non-conformities. Such spurious outcomes would bring the whole system into disrepute, although it is probably more likely with 100 per cent samples.

Skip-lot rules would apply only to situations where there was a long series of passes, and would permit a stepwise progression through 1 : 1, 1 : 2, 1 : 3, 1 : 4 randomly selected datasets. Failure of a dataset would cause a return to the previous level of auditing or even a complete cessation of skip-lot sampling. This approach is mentioned in the BS, and a supplement giving the actual rules is expected. If such skip-lot procedures are implemented, then it would be prudent periodically to review the control procedures used by the dataset producers and to inspect for continued compliance with them.

### 32.5.3 Systems Based on Limiting Quality

The ideal sampling system would accept all datasets whose quality was better than or equal to the acceptable quality limit and reject all others. The relation between chance of acceptance and quality

would be as in Figure 3. This is rather like a perpetual motion machine, in that it is possible to approach this ideal but never to achieve it.

Diagrams such as Figure 3 are very useful, in that they express the relation for each sample between quality of the dataset and the expected audit result. The British Standard was constructed around a high chance of accepting lots of a suitable quality.

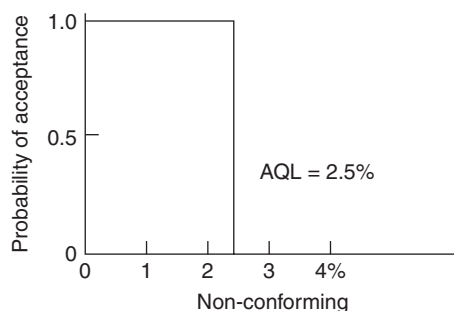
An actual diagram is shown in Figure 4. BS 6001 is built around the ‘shoulder’ of the curve, which usually indicates a probability better than 0.90 of accepting datasets if the presenting quality is equal to the AQL.

It is subject to one difficulty, however. There is a small (but not insignificant) chance of lots of a quality which are far from acceptable being passed. Concentration on the acceptance of high quality described by the shoulder of the curve sometimes draws attention away from the ‘toe’ of the curve, with serious results. It is the toe that shows the chance of datasets with grossly unacceptable numbers of non-conformities actually being passed by the system. For some sample schemes, particularly those involving small lots, there are chances in the range of 0.05–0.10 of accepting datasets with a quality  $5\times$  to  $10\times$  worse than the acceptable level. For many applications this is fine, but in data auditing it can be a problem.

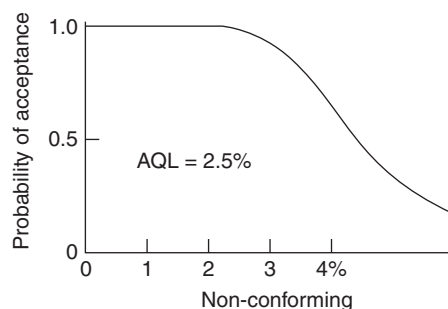
It is possible to design sampling schemes where the main objective is to reduce, as far as possible, the risk of very poor quality datasets being accepted. The consequences are enhanced levels of sampling and more regular spurious rejection of adequate datasets. This type of scheme is based on ‘limiting quality’ in contrast to the ‘acceptable quality’ schemes which have formed the basis of this chapter. Limiting quality systems are dealt with in Supplement 1 of the BS 6001, 1984.

### 32.5.4 The Isolated Dataset

The basis of the sampling schemes is the production of a continuing series of datasets. Protection against non-conforming data is provided by the switching rules, which allow the system to react to such a drop in quality.



**Figure 3** Relation between chance of acceptance and quality



**Figure 4** BS sampling diagram



Where datasets are produced in isolation, as might happen when a contractor is used for the first time, then particular caution is required. The system is adaptable to this situation, using the limiting quality approach. This focuses attention on the chances of single batches, possibly of very low quality, being presented. In these circumstances the more extensive sampling is clearly justified, and possibly a period of 100 per cent sampling would be appropriate. The user must decide the balance of risk and cost when the decision to use a new production process is made. An inspection of the new facility and a comparison of its procedures with those of the sponsor will facilitate the decision. While QA can advise on this, it is for management to decide on policy and live with the consequences.

### **32.5.5 Bespoke Systems**

There is no unequivocal reason why sampling schemes should be based around either acceptable quality or limiting quality. It is possible to design systems around an indifference level, where there is an equal chance of a specific quality being accepted or rejected. With a degree of selection, such schemes may be able to satisfy limits of both adequate quality and limiting quality. This raises the possibility of control of both acceptable quality and 'rare rogue' datasets. Such systems require specialist support, often the services of a consulting statistician. Irrespective of the nature of the system, it is important that there is agreement between producer and user on the criteria for acceptance and the procedures used to ensure their achievement.

### **32.5.6 Other GLP/GCP Applications for Sampling Procedures**

While data auditing is the chief example of a series of repetitive tasks for an auditor, there are others, particularly in toxicity studies. Among these are inspections of very short-term studies, Ames tests and LD50 tests, which are often run as production lines. The selection of particular phases for inspection and the sampling of such a series could benefit considerably from the structured approach outlined for dataset auditing. The main benefit would be the quantification of the results of audits, which would assist planning and provide a justifiable basis for the sampling method.

## **32.6 CONCLUSIONS**

Statistical sampling schemes offer benefits to both dataset producer and dataset user. For the QAU they provide a structure for inspection and auditing. They are easy to use and provide a quantifiable result. As such, they considerably enhance the value of the records of quality assurance.

When inadequate quality is identified in a sample, the implication for the whole dataset is clearly quantified. The limit of acceptable quality is agreed beforehand, and the history of recent batches is available. This environment allows rational decisions on the actions required, in marked contrast to the reaction engendered by the unanticipated discovery of flaws in datasets which have been subject to spot checking only.

The use of statistical sampling schemes will sooner or later turn up cases of unacceptable quality, and the process for deciding their fate can be agreed in advance. The choices lie between disposal and reworking. In the latter case the dataset should be fully re-audited.

Statistical sampling schemes are to some extent self-controlling, in that they respond to quality trends. Consistently good results allow relaxation of sampling. Bad results lead to tightening and even suspension of sampling in favour of 100 per cent checking and/or an overhaul of the process of document production.

## **FURTHER READING**

1. American National Standard ANSI Z1.4.

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## Metrics and Trend Analysis

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### 33.1 INTRODUCTION

A great deal has been written on the subject of statistical methods for quality control (QC) and Quality Assurance (QA). Major contributors to this who have been included are as follows:

Deming was particularly influential in the use of trending methods to control the variability of manufacturing processes.

Joseph Juran produced an influential reference work on QC that covers most of the statistical methods applicable to this field.

Crosby defined quality as ‘conformance to requirements’. This could be translated in the GXP-regulated areas as ‘compliance’. He also coined the term ‘zero defects’ as being the ‘performance standard’ – perhaps equivalent in regulated areas as 100% compliance.

A useful condensed guide to these, and other, quality ‘gurus’ is shown in ref. 1. In the areas of Research Quality Assurance, the main uses of statistical methods appear to be:

Sampling and decision-making

Trend analysis and comparisons (often referred to as ‘Metrics’).

### 33.2 STATISTICAL SAMPLING AND QUALITY DECISION-MAKING

Sampling methods are important when QC/QA professionals are required to look for defects (errors, non-compliances, *etc.*) in data sets or activities that are very large and/or very complex. In these situations it may not be feasible to check every item. The QA and QC professionals are then faced with assessing quality by checking less than 100% of items/activities. In such circumstances it may be important to obtain an estimate of the number of defective items that remain in the data/activities that were not included in the sample and, hence, were not checked.

Statistically based methods, usually employing random sampling, and the laws of probability, attempt to give a measure of the risk that the sample selected was not representative of the whole, and then use the outcome from the sample check to make an inference about the quality and acceptability of the whole.

The most common use of statistical sampling in GXP is in the auditing of data sets, either in databases or in report tables.

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<sup>†</sup>The author is indebted to Ian Oulsnam (MHRA) who had written a previous article in QUASAR and provided helpful comments on an early draft of this chapter.

In previous editions of Carson and Dent, Townsend gave a detailed analysis of the use of the British Standards (BS) 6000/6001 in data audits.<sup>2</sup>

These standards were originally developed for sampling the output of manufacturing processes, in order to assess whether the *quality of the process* remained within acceptable limits or whether the process was producing more defects than was acceptable.

It is important to understand that BS 6000/6001 is primarily looking at the quality of processes and is less interested with accurately assessing the quality of individual batches.

In GLP and GCP terms, BS 6000/6001 would be giving its most reliable information on the process of database/report table production, but would give less reliable feedback on the quality of data in individual databases or reports.

Often, the basis of statistical (quality) sampling schemes is as follows:

An upper level is defined for an allowable proportion of defects (*e.g.* in the data sets). This is often referred to as the acceptable quality level or limit.

A sample size is calculated such that it is likely to contain sufficient errors that would lead to rejection if the true proportion of defects is above the stated acceptable level. The sample is then taken randomly from the total population (as in the data). If the sample is not taken randomly then the assumptions on which these schemes are based become invalid. It is checked for defects and the number of defects is counted. The number of defects is then compared with the number of defects expected at the limit of acceptability. If the sample contains more than the limiting number of defects then the batch (report, database, *etc*) is rejected.

#### *Example*

A required upper limit for defects (quality standard) is 5%.

If we take a (representative) sample of the size of 300, from a batch that contains exactly 5% defects, we would expect the sample to contain  $300 \times 0.05 = 15$  defects. So, our upper limit of quality could be set at 15 defects.

If a particular set of data actually contains 6% error (0.06), we would expect to find  $300 \times 0.06 = 18$  errors when we check our sample. Since this is above the limit of acceptability ( $18 > 15$ ) we would be led to reject this set of data.

In practice the number of defects captured would vary from sample to sample. Assuming random sampling, this variance can be calculated. The acceptable limiting number of defects can then be set to ensure a low risk of incorrectly passing a batch (set of data) that should have been rejected.

It should be noted that the BS 6000/6001 sampling scheme on 'normal' levels will often pass batches that contain slightly more defects than the stated 'AQL', or quality level.

### **33.2.1 Detecting Systematic Errors with Sampling Methods**

One weakness of sample checking relates to the identification of systematic errors. This is even more pronounced if the sample is very small in proportion to the entire batch/data set. For example:

Data sets are often tabular in form, and data elements within rows or columns may not be independent from each other. For example, in tables of haematology results for a group of patients, the same systematic or procedural error may have affected all data elements in some rows or columns.

When a sample includes only a maximum of one element from each row or column, it would not be immediately clear whether an identified defect was an isolated problem or if it was part of a larger systematic or procedural error.

A simple improvement on checking only the data sampled would be to check additional data surrounding any defect identified in the sample. In this way it would be possible to assess whether any defect discovered in the sample is an isolated defect or if it actually belongs to a bigger systematic error.

### 33.3 METRICS – COMPARISONS AND TREND ANALYSIS

The most common use of metrics in GXP is to keep track of the number of findings that arise from audits of particular activities, processes or systems.

A recent survey of members of the British Association of Research Quality Assurance reported that most companies responding (45 responses from 40 companies) were interested in making use of audit metrics, although only 56% were actively doing so. The most common approach to producing audit metrics is to list findings from audits and to categorise them in some way. It is also common to have some weighting system for the findings to indicate severity.

These metrics may then be used for simple comparisons, for example:

Comparing numbers of findings between studies, investigator sites, projects or other factors of interest, within a given period of time.

Comparing the number of findings in a particular item/activity over time, in order to identify changes in quality/compliance. This approach is often called 'Trending'.

The comparisons may be by the gross number of findings, by weighted severity of findings or by findings of a particular type such as protocol non-compliance, SOP non-compliance. More ambitious schemes may even concentrate on narrow, but important, findings of non-compliance such as failure of investigator sites to report Serious Adverse Events within a given time.

While the preceding approach has the advantage of identifying specific items/activities needing correction, it has severe limitations with regard to making statistically meaningful comparisons and trend analysis.

#### 33.3.1 Disadvantages

Subjectivity of findings – There may be differences between auditors in assessing the severity of a finding, even whether or not a finding exists or should be reported. This can invalidate attempts to make comparisons between individual audits or groups of audits. For example, it can be difficult to separate audit effects from process effects – a lower number of findings from one group of audits could reflect higher quality of the processes audited or, less thorough auditing!

Negative – Simply analysing audit findings (faults) gives only an indirect measure of quality; it does not directly measure the degree of acceptability of procedures/items audited. Listing faults is demotivating for the auditee – telling them how they compare to a defined ideal is far more motivating.

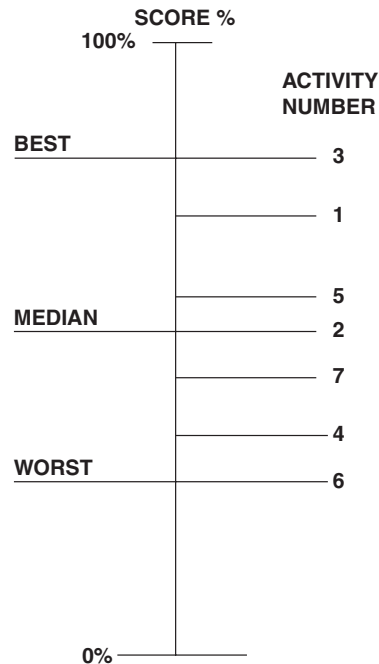
Accuracy of measurement – As systems/procedures improve, there will be fewer findings. Smaller numbers (of findings) lead to less reliable statistics. A positive measure (% ideal) provides more information for analysis.

An outline of a more powerful approach is given below.

### 33.4 A POSITIVE AND OBJECTIVE APPROACH TO METRICS DERIVED FROM AUDITS

- (i) *Identify* procedures/activities/documents that are key to the quality of the process to be audited.
- (ii) *Define* a set of quality requirements for each of these activities or items (*e.g.*: List of all documents required in a particular file, dosing compliance, core protocol requirements, completed informed consent forms, accuracy of data recording, *etc.*).
- (iii) *Score* each activity/item, during the audit, in relation to the defined requirements, using a common scale. (*e.g.*: % required documents present, % dosing compliance, % core protocol compliance, % accuracy of data.)
- (iv) *Rank* the activities by score.

- (v) Summarise the ranking by Best, Median and Worst score as follows -

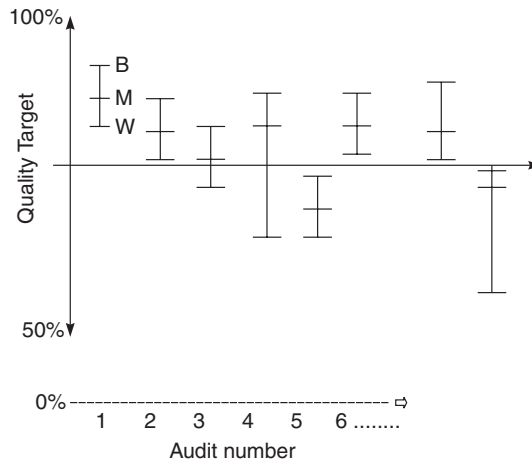


The B (best score) statistic shows how well the best activities perform. The M (median score) statistic is the mid-range score for activities audited – half of all activities are better than this score. The W (worst score) statistic indicates the worst level of performance.

- (vi) Make *comparisons* between audits or sets of audits (time periods, geographical areas, projects, *etc*) by statistical analysis of differences between BMW scores (or mean BMW scores for sets of audits) and of differences in the ranking order of different activities.
- (vii) *Chart* the BMW scores for each audit to provide trend analysis charts.

### 33.4.1 Trend Analysis

Plot BMW statistics against time course of audit and look for trends.





### 33.4.2 Audit number

From the preceding chart it can be seen that all activities in the first two audits have scores above the notional standard (defined by R&D management). The third audit has detected a few under-performing activities (although more than half are acceptable:  $M > QT$ ). Audit number four metrics indicates a good facility with one or two problem areas, and audit five observed failure of the facility/process to meet quality targets for any activity.

In addition to monitoring the BMW scores, it is important to monitor the B–W, M–W distances in order to assess the consistency of activities at site:

The ultimate would be  $B = M = W = 100\%$  scores.

Large B–W differences indicate poor control of quality.

Good M scores with large M–W differences indicate a good facility with some problem areas.

A continuing reduction of B–W difference, assuming B remains a high score, is evidence of a positive learning process.

The method of ranking scores for key/core activities is particularly useful when comparing groups of audits from several time periods, geographical areas, projects, *etc.* This could be done by taking the mean scores for activities within each group of audits and then ranking the mean scores. Comparison would then be made of group mean scores for particular activities, or of overall group mean BMW scores.

### 33.4.3 Summary of Advantages

- (i) Positive feedback – facility/project management is shown how well they are performing, rather than just receiving isolated lists of failings.
- (ii) Consistency – objective measurements taken with respect to a common definition of quality should lead to consistency among auditors' assessments.
- (iii) Provision of an overall statistic for quality at an audited facility. This can be captured immediately after audit completion and added to a continuous trend analysis chart.
- (iv) More statistical power for analysing trends or differences between groups of audits. This arises from using measurements that have range rather than using categorical findings.

## 33.5 SUMMARY OF THE USE OF STATISTICAL METHODS IN RESEARCH QUALITY ASSURANCE

The use of statistically-based sampling methods can provide an auditor with a measurable amount of confidence in the outcome of a sampling-based audit, since the risk of obtaining unrepresentative samples can be set at an appropriately low level.

Statistical methods can also be applied to audit findings in order to give meaningful and robust comparisons between types, or groups, of audit. Such comparisons can be made over intervals of time, in order to provide trend analyses that can be tested for statistical significance.

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# Supplier Auditing

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## 34.1 INTRODUCTION

The practice of auditing suppliers is an important activity that is expanding in response to regulatory and commercial needs. Essentially auditing is a process whereby pharmaceutical customers seek to understand how they can reduce risks to their customers and/or company that may arise from either a supplier's underdeveloped quality system or product or from an adverse regulatory reaction. It is a form of insurance. While regulatory expectations for audits are clear in some areas, in many others they are not, which means that the pharmaceutical company must develop its own risk assessment process, perform the selected audits and obtain value from them. This requires an integrated and long-term approach that will involve stakeholders in several departments within a company, the selection of auditors who will be able to audit effectively to the appropriate standard and the involvement of the supplier to maximise any necessary improvement process. The chapter covers many of the principles to be considered in the management of this important process.

## 34.2 WHEN SHOULD YOU AUDIT A SUPPLIER?

The responsibility for the pharmaceutical company 'to approve and monitor suppliers of materials' is clearly defined in clause 2.7 of the EU good manufacturing practice (GMPs) rules.<sup>1</sup> However, the decision as to whether such monitoring should extend to auditing a supplier is an important one that should be taken after careful consideration of a range of criteria that can have relevance to the specific situation faced by the organisation. An organisation may be acting in a preventive mode or a reactive mode and both have validity within the overall management of the quality of supplied pharmaceutical materials or services. While a well-developed audit programme will be biased towards preventive auditing, time must always be found to be able to react to the unexpected problem or commercial imperative.

However, in order to avoid the situation of always being in the reactive mode of perpetual firefighting, which can be dispiriting and commercially expensive, it is essential that a well-developed preventive plan be developed. This plan should be based on a cycle of auditing that should stretch over several years and be based on a policy that has been debated and accepted by key stakeholders within the organisation. Primary stakeholders who should be included in the development of this policy should include representatives of Engineering, Production, Purchasing and Quality Assurance (QA). This list is not exhaustive and may extend to other groups such as development units, where new products are involved or the computing department where computerised systems are used in quality critical processes.

It is also important for large organisations to attempt to integrate the interests of different parts of their organisations to avoid the potentially embarrassing scenario where the supplier points out that someone from the same company conducted an audit recently. Such embarrassment would of course be exacerbated if the supplier politely pointed out that different audit standards were being applied. Avoiding such incidents will require a degree of internal mutual trust and co-operation that may take some time and effort to develop. It is probable that this trust will only become sufficiently developed when auditors from different parts of the same organisation experience each other's audit processes.

The audit policy that is developed will necessarily be specific to each organisation but a number of generic factors should be considered. The expectations of regulatory authorities can have a major impact, depending on the particular sensitivity and experience of the authority involved. There is no substitute for seeking to understand what these expectations are and while an introduction to this subject is provided later in the chapter, the audit plan owner should stay aware of current GMP trends on this subject. The trend over the last 20 years has been for such expectations to gradually increase.

Where an audit is not mandated by a regulatory authority, a helpful tool used by many organisations is to perform a risk assessment for each supplier/material combination. This assessment should consider the risks to the business and patients of a failure to detect a potentially defective batch of material either within the supplier's quality control (QC) system or the pharmaceutical company's QC system (Chapter 30 by Newton). It is not enough to only consider each supplier, as alternative types of materials manufactured by the same supplier could have widely differing uses.

For example, a supplier may supply printed cartons, patient information leaflets (PILs) and labels. With leaflets, it is very important that each side is printed and there are no blank sides so that every patient understands how they should use their medicine. This problem would not occur with either labels or cartons as they are not printed on two sides but such blanks can occur on leaflets if two sheets of paper pass through a print station simultaneously. It is highly unlikely that they would be detected through conventional sampling and QC sampling techniques, so assurance of the very high performance required must rely on automatic prevention or detection systems installed on the supplier's printing lines. Such assurance is usually achieved by understanding the critical risks and auditing the systems designed to protect against them occurring.

A set of alternative approaches for managing the mix of controls available to the organisation for different supplier scenarios is shown in Figure 1.

A rationale for making the decisions required must be based on good data. This requires that metrics should be in place to assess 'Confidence in the Supplier'. Typically, this will include an assessment of the extent of development of the supplier's quality system, combined with a measure of delivered performance for each material. This important measure should include measures of incoming defective batches, feedback from production performance and any customer complaints that are attributable to supplied materials. The measure should be normalised on the volume of material received, using either batches or parts per million, to enable both comparison with other suppliers and measure progress over time without distortion due to changes in received volumes. Monitoring moving annual averages or cusums can be a powerful aid for viewing emerging trends and can be useful in providing trigger points for action.

The question of how often audits should be scheduled is one that should evolve from the risk-assessment process. Typical frequencies employed are for suppliers of critical materials to be audited at least annually, whereas suppliers of low-risk materials might be audited every 3 years.

The amount of time typically 'allowed' by a supplier for a second-party audit is 1 day, but this could be extended for critical/high-volume supply situation. This time is usually considerably less than the times recommended by the International Accreditation Forum for third-party certification audits. Pharmaceutical companies should always maintain the capability to respond to urgent situations that require evaluation and dialogue with the supplier.

Confidence in the supplier	High	1. Very low/zero frequency of audits 2. Encourage development of supplier's system 3. No change in QC at supplier 4. Consider reducing QC on receipt	1. Maintain high frequency of audits 2. Encourage development of supplier's system 3. Maintain high frequency of QC supplier 4. Consider reducing QC on receipt
	Low	1. Low/zero frequency for audits. 2. Encourage development of supplier's system 3. Increase QC at supplier. e.g. Increase the sampling frequency 4. Maintain QC on receipt but increase if defects not detected before use.	1. Very high frequency of audits 2. Insist on development of supplier's system 3. Increase QC at supplier. e.g. Increase the sampling frequency 4. Increase QC on receipt 5. Consider additional in process control checks 6. Provide regular feedback on progress to supplier 7. Consider alternative supply if progress is inadequate
		Low	High
		Risk to the business or patient	

**Figure 1** *Alternative strategies for different supplier scenarios*

### 34.3 REGULATORY EXPECTATION

The current trend of regulatory expectation is for an increasing level of assurance to be obtained in the quality of supplied materials and services. This appears to be an understandable response to experiences of quality defects in medicines that have originated outside the pharmaceutical facility or deficiencies observed in quality systems. The following examples illustrate the breadth of this concern and also highlight certain GMP clauses where audits are specifically required.

In 1996, at least 59 children in Haiti died of acute kidney failure as a consequence of being given paracetamol syrup contaminated with diethylene glycol. While the contaminant had been present in the intended excipient glycerol at up to 29%, it had not been detected by the pharmaceutical manufacturer's QC laboratory on receipt. An informative and helpful article<sup>2</sup> published by the UK's MHRA (MCA) emphasised the importance of rigorous control of labelling of such chemicals by suppliers. This was clearly a message directed at the pharmaceutical industry, as most regulatory agencies have neither the resource nor the authority to audit excipient suppliers.

European regulators have also emphasised the importance of auditing suppliers in Annex 8 of the EU GMP rules when pharmaceutical manufacturers are considering a reduction in the amount of identity testing they perform. The current EU requirements are that each container should be identified. This is an onerous requirement that frequently stresses the capacity of QC units. A prospective way through this problem is provided by the regulators in the Annex, but this requires 'regular audits of the manufacturer's Quality Assurance system . . . '.

Personal experience gleaned from US Food and Drug Administration (FDA) inspectors has consistently reinforced their concern regarding the security of distribution systems. They see this as

a vulnerable area, where they look for assurance derived from audits conducted by the pharmaceutical manufacturer, that the distribution system is secure from deliberate attempts at malicious contamination. Related concerns have also prompted the World Health Organisation (WHO) to issue draft guidelines<sup>3</sup> for GMPs appropriate to the whole distribution chain for starting materials because 'Experience has shown that especially activities such as repackaging and relabelling create increased risks for contamination, cross-contamination and mix-ups'. A key requirement (14.2) of this guidance expects an audit when it states that 'The contract giver should evaluate the proposed contract acceptor's compliance with Good Trade and Distribution Practice (GTDP) before entering into an agreement'.

The gradual introduction of computerised process control and information management, the use of electronic approval and data transfer processes has inevitably attracted increasing attention as risk areas are identified. The basic EU GMP requirement in Annex 11 is to take reasonable steps to ensure that it (the software) has been produced in accordance with a system of 'Quality Assurance' – *i.e.* more auditing. The subject of 'Computerisation' is discussed further in Chapter 37 by Nelms.

A commercially damaging product defect incident that involved the recall of 1 million asthma inhalers was reported by the MCA in 2002, as because of faulty valves. The complexity of such components and the critical role they have in assuring that medicines used for the relief of a condition that can be fatal if not treated effectively. This complexity has been specifically recognised within Annex 10 of the EU GMPs, which covers the manufacture of pressurised metered dose inhalers, when it states that 'Auditing of the Quality Assurance system of the valve manufacturer is of particular importance'.

While the CFR, Part 211<sup>4</sup> makes no specific mention of auditing suppliers, the FDA has had a long-standing concern regarding the quality of active pharmaceutical ingredients (APIs). It has consistently allocated approximately half of its overseas audit resource to this topic, whereas in the EU the auditing of API manufacturers has relied on a voluntary scheme. However, it is anticipated from draft EU legislation that inspectors will gain the authority to audit both API manufacturers and, learning from the transmissible spongiform encephalitis (TSE) outbreak, suppliers of other excipients that are considered to be critical.

Another factor that has caused a tightening up of expectations is the mutual recognition agreement (MRA) process that is currently in progress. This involves observation by one nation's inspectors (say the United States) of another nation's inspectors (say France). An inevitable consequence of this mutual monitoring process is that there is less tolerance of deviations from designated GMPs.

The position of inspectorates in respect of viewing the contents of supplier audit reports is the same as for internal audit reports, in that they will only insist on seeking reassurance that an audit has been completed. This policy will often take the form of asking to see that the report exists, but it is the accepted convention that they will not ask to see the contents. The reason for this is that inspectors appreciate that if they start asking to see the contents then organisations will tend to massage these contents, which could have an impact on their effectiveness.

Finally, inspectorates expect to see that all suppliers whose products or services can have an impact on product quality have been formally approved by QA. This places a responsibility on QA to be able to defend these approvals whether they have been audited or not.

### 34.4 WHAT IS THE APPROPRIATE STANDARD FOR AUDITING?

Selecting the appropriate standard that will be used for an audit is paramount. There is a wide range of standards available that have been published and these are continually being revised. Most are based on either the GMP or ISO 9001:2000 frameworks. The auditing organisation may alternatively have developed its own audit standard, which may expand on an existing standard. The key principles that should be borne in mind here relate to the appropriateness and openness of

the standard. For example, if an organisation wanted to assess the customer focus of a potential supplier, it would probably want to ensure that elements of the new ISO 9001:2000 standard (which is much better than EU GMP in this respect) were employed. The standard selected should be recognisably appropriate for both the customer and the supplier and it should be available to the supplier prior to the audit.

For example, a pharmaceutical company may wish to audit the supply chain for a starting material excipient being sourced from China. Appropriate standards to consider are PS 9100,<sup>5</sup> which covers manufacturing and agents and the WHO Good Trade and Distribution Practice draft guideline that covers distribution. The supplier should be always be advised well in advance of the standard and provided with a copy if needed.

### 34.5 WHO SHOULD AUDIT THE SUPPLIER?

This is a very important question on which the effectiveness of the audit process will depend enormously. It is very rare, if not unknown, to find an auditor who has the competence to audit all types of supplier, or audit to a range of standards. Consequently, the representative(s) selected for each type of audit should have skills and knowledge appropriate to the product or service provided.

While a member of QA will usually initiate the audit process, it is very important that the decision as to who the auditor(s) should be involves colleagues in other appropriate departments such as Development, Microbiology, Production, Purchasing and Engineering. The question of how many auditors should be involved can usually be answered after careful consideration of the audit plan. Writing this plan down well in advance is the key, as it requires a clear understanding of who will be auditing which clauses and of which standard.

A second key question to ask is 'What do we need to understand better?' For example, the organisation may want to understand whether they can be confident that a prospective contract-testing laboratory will deliver reliable results for a product under development. In this case, the auditors might be representatives of the Development Unit's Laboratory team and a QA audit specialist, who jointly understand the requirements for the performance of the analysis, communication and appropriate elements of GMP. They should define clearly how they will achieve this early in the process. Again looking at the clauses carefully *in advance* is invaluable. No clause should be audited unless it will provide useful information.

Another common audit situation is where a company needs to monitor the quality system of an established supplier of materials used regularly in manufacture. An example might be printed labels. In this case, the audit could be performed by a single auditor, skilled in the appropriate supplier GMP standard (*e.g.* PS 9000<sup>6</sup>) and familiar with the supply sector.

Another scenario might involve a planned change of manufacturing location by a supplier of a critical excipient<sup>7</sup> made using a process that was specific to the customer. This is a complex issue that raises questions concerning the risks to supply from the current location, which purchasing colleagues would seek continued reassurance on. It also raises questions concerning the quality of the system used to control the manufacture of the excipient at the new facility. This would prompt the involvement of an auditor skilled in PS 9100. Finally, the nature of the process might prompt a validation specialist to audit the proposed process to understand the implications for revalidation.

These examples serve to illustrate the range of questions that can arise and usefully show how the number and skills required by auditors will vary with each scenario.

### 34.6 HOW DO YOU CONDUCT AUDITS?

The subject of learning how audits should be conducted is an enormous one that is normally addressed by a combination of reading, in-house training and attendance on external courses. The manager considering which type of training to select has a number of different options to consider,



ranging from ‘accompanying the current auditor’ to attendance at a week long internationally recognised course such as a ‘Pharmaceutical Lead Assessor’ course. Each option can deliver training of value. The primary options to consider are as follows.

### **34.6.1 Accompany the Current Auditor**

This method is very common and often the entry point for people new to auditing. The novice will quickly experience the wide range of skills they will need to become competent, ranging from listening to time management. Learning from an experienced auditor and given opportunities to practice, supported by constructive feedback, the novice will learn fast. This process can be strengthened by providing guidance on auditing that might take the form of company standards, policies and guidance or published guides such as the Pharmaceutical Quality Group’s (PQG) monograph.<sup>8</sup> However it can be difficult to provide a recognised competency assessment using this route.

### **34.6.2 Run an Internal Training Course for New Auditors**

This method will take longer to organise but has the advantage over the first option in that audit practice performed by the novices can be done in a risk-free environment where it does not matter if they make what might otherwise be potentially embarrassing mistakes. It also has the advantage that discussion of difficult, confidential or other company issues can be facilitated throughout the training. Role play can be a valuable part of this process, which can be combined with training for auditees on how to react during an audit. The power of such role plays can be accentuated if video footage is taken and subsequently reviewed with the auditor. An internally run course could also be designed to assess the competency of trainee auditors, with the help of the ISO guidelines for quality auditing.<sup>9</sup> This guide provides in Section 7 useful sets of checklists covering the personal attributes and knowledge and skills that are considered appropriate for auditing. It also includes a number of other useful checklists that should help in the development of an organisation’s audit process. For example, guidance on what to cover during the opening and closing meetings is highlighted.

### **34.6.3 Attend an External Accredited Course**

Attendance at a recognised course offers some significant advantages that merit consideration. Courses such as a ‘Pharmaceutical Lead Assessor’ course<sup>10</sup> are based on PS 9000 and PS 9100, which integrate GMPs appropriate to suppliers of pharmaceutical materials into the internationally recognised ISO 9001:2000 framework. ISO 9001:2000 is the *de facto* quality system standard for a wide range of suppliers and current experience shows that over 90% of suppliers to the European pharmaceutical industry are certified to it. Consequently, the vast majority of the quality manuals that an auditor will see will be based on this standard and he or she will need to understand the language of ISO 9001. An excellent way to achieve this would be to attend a lead assessor course. A further significant benefit of these courses is that the discipline required to be demonstrated by the auditor during the course should improve their confidence and hence their performance in what can be a demanding role.

An additional benefit can come from the exposure the attendee gets to auditors from different organisations. Such interaction can open the minds to new and better ways of working, which may enable the returning attendee to influence his or her organisation for the better.

It is recommended that new auditors attend such a course but only after they have learned the basics of their company approach from colleagues, have shown some basic competence and are determined to develop their skills. All of the accredited courses have a final assessment, so a ‘pass’ is an externally recognised attainment of competence.

### 34.6.4 Auditing to Good Manufacturing Practice

This is the most difficult scenario to manage and requires that the auditor selected should have been exposed to GMP standards for a considerable period. As the subject is so large, it will usually often be necessary to select auditors who are specialists in the appropriate subject, *e.g.* good laboratory control practice, clean room standards, TSE and electronic signatures.

Of paramount importance, regardless of the type of audit, is the need for each auditor to brief all stakeholders on the scenario of the outcome, the implications and the follow-up process. The understandings achieved must be shared to release their maximum value. This step is crucial to help convince the various stakeholders that they are getting good value for their insurance premium – the cost of audits.

## 34.7 THE BENEFITS OF AUDITING SUPPLIERS

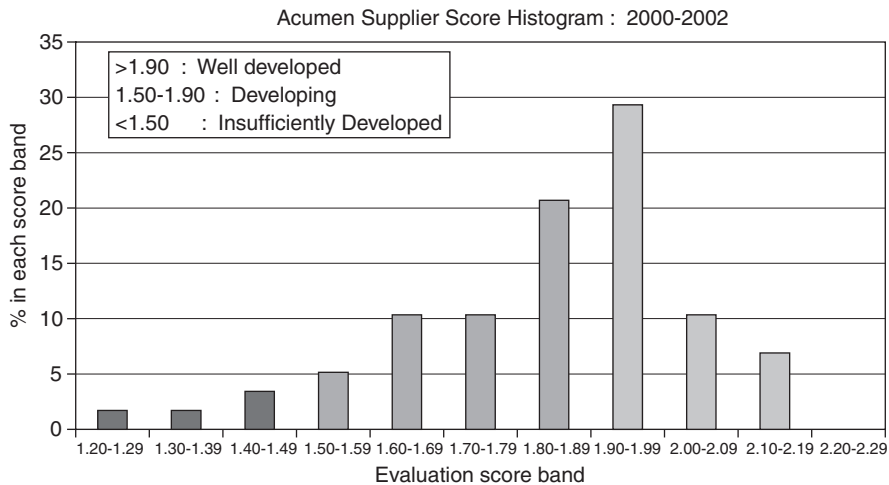
Initially supplier audits are usually arranged to meet the GMP compliance expectations of regulatory authorities, but this changes with increasing experience. It is a common experience of auditors (and their managers) that as the mutual understanding grows between the supplier and the pharmaceutical industry customer, the quality of the supply performance and the supplier's quality system tends to improve. This would be expected to show up as an improving trend in defect rate of supplied materials measured, which should be measured for all key materials. This experience is reflected in the valuable research performed in the United States by Raju and Cooney.<sup>11</sup> The careful measurement of each supplier/material history enables the pharmaceutical company to manage their supply base with more clearly delineated strategies.

For example, a key decision might be whether the organisation should continue to purchase materials from a particular supplier. The creation of a policy, which defines minimum acceptable levels of performance for both the quality of the supplier's system and a measure of the quality of supplied materials, can be very helpful. Such measures, which if evaluated in addition to commercial considerations such as responsiveness, price and reliability of delivery, contribute to a holistic appreciation of the overall competence of the supplier – which can then be compared with the alternative sources of supply. A very useful approach is to convert each set of audit findings into a semi-quantitative overall score for the system. This can then be plotted as a histogram for each supplier in the supply base. An example is shown in Figure 2.

Trigger points can then be selected for key decisions. For example all suppliers, whose audit score is less than 1.5 in Figure 2, would be considered as insufficiently developed. This would then prompt the decision to either look for an alternative supplier or, if this was not possible, to work very closely with the supplier to improve their system. At the other end of the histogram, those suppliers whose systems scored highly (*i.e.* above 1.90) would be considered as well developed. Such suppliers would be among the first to be evaluated when seeking to introduce a reduction in incoming QC testing by acceptance of the supplier's certificates of test (analysis). An analogous set of metrics could be developed for supplied performance that could include key parameters such as batch defect rate, production feedback and customer complaints. This type of approach, while intuitively obvious, requires considerable resource and persistence to implement. However, experience and findings from the US benchmarking exercise<sup>11</sup> have shown that rewards such as reduced inventory (hence capital costs) and QC costs, improved supplied performance and shorter lead times, can be significant.

## 34.8 TREAT THE SUPPLIER WITH RESPECT

Suppliers are the experts at manufacturing the products they supply, but this is often not reflected in the way they feel that they are treated by representatives of the pharmaceutical industry. Stories



**Figure 2** *Acumen supplier score histogram for 2000–2002*

of arrogance displayed by such representatives are still quite common and essentially this type of behaviour is destined to produce relatively poor returns for the auditor. He or she may get compliance, but even that will be compromised and the highest possible returns that come from an open approach-based on mutual respect will not be achieved. This subject is dealt with well in the PQG monograph on auditing, but the crucial insight needed is to try to appreciate how the auditor would respond to the way the audit is conducted. This is not easy but a good start for the auditor is to ask himself or herself the question ‘*Do I like to hear only negative comments?*’ We all respond the same way!

Common sense therefore says that the obvious behaviour for the auditor to adopt is to commend the supplier’s system frequently and whenever a positive attribute is detected. The auditor will observe many of them during the audit process and if he or she has been commenting positively on them throughout the day, then the auditee will be more inclined to accept with a positive attitude the relatively smaller number (hopefully) of non-conformities that will probably be detected. A good auditor may also be able to offer helpful overviews of what appear to be unnecessarily different ways of working within the audited company. Using this balanced approach makes all the difference to motivation, as does making a point of finding out each auditee’s first name and using it often.

One supplier practice that is becoming more prevalent, as the demand to audit increases, is for suppliers to seek to refuse audits where the volume of business involved is low. While some suppliers see audits as free consultancy, others are audited so frequently that they view them as too time consuming. Alternative strategies used by suppliers to minimise such costs include setting quotas, outright refusal, insisting on joint audits, offering third party audit reports or responses to questionnaires only or simply delaying arrangements. The auditor is recommended to understand the commercial background to each prospective audit before he or she approaches the supplier and discusses any response of this nature with their purchasing colleagues. There may not be an easy answer but obtaining some form of information is usually possible.

Other good practices that will reinforce the value of audits and improve their effectiveness are providing suppliers with feedback on progress, recognising good performance and offering help with training.

Providing feedback on progress on the performance of the supplied service/material will help both the supplier and customer understand whether they are on track or not. It is especially

motivating if it shows positive signs. Once a performance goal has been achieved, the provision of a certificate or letter by the customer, which recognises the achievement, should help reinforce that motivation. Empathy on the part of both parties will be improved if the customer offers to help with appropriate training or awareness. This can be either at the supplier's premises or could involve inviting supplier's personnel into the pharmaceutical plant. This can be particularly valuable when improvements are needed, as seeing the GMP standards within the pharmaceutical plant where their materials are used should help the acceptance process.

Finally, a factor that can be extremely valuable in accelerating a post-audit improvement programme is the nature of the prospective commercial relationship that is likely to exist. Essentially, the more confidence that the pharmaceutical customer can provide of an ongoing future business relationship, the greater the chances of success. Companies will frequently offer long-term contracts for suppliers of key materials, which are seen as mutually beneficial by both parties.

## ACKNOWLEDGEMENTS

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## Centralised Supplier Audits for Animal Studies

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The OECD Principles of GLP indicate that a study plan should contain detailed information about the test system used (plant, animal, bacterium ...). Furthermore, Environment Monograph 111 states that, among other objectives, a regulatory compliance monitoring inspector should assess records to ensure that they are appropriate to the receipt of test systems, their health, behaviour, disease diagnosis and treatment, and so on. EEC Directive 2004/10 is similarly comprehensive in requiring proper housing, handling and monitoring. None of these texts, it should be noted, requires that suppliers should be audited. However, it is an explicit responsibility of test-facility management to “ensure that test facility supplies meet requirements appropriate to their use in a study”.

While it is eminently possible to perform checks on suppliers of basic supplies such as animals, feed and bedding in a restricted sense, by relying on those suppliers' own advertising material, this will not be viewed as satisfactory in the event of a supply-related compliance issue. There is a tacit expectation that test facilities will go much further, and for many years inspection by a regular visit to such suppliers has featured in all well-developed QA programmes.

In 1990 the French Quality Assurance Society (SoFAQ) began discussions with selected suppliers with a view to reducing the frequency of visits by its member companies and replacing these (at least in part) by a centralised, national auditing scheme. As there existed in France a national animal-supplier group, Groupement des Eleveurs et Fournisseurs d'Animaleries (GEFA) they were the first to be approached to develop and ratify yardstick guidelines on the performance and reporting of such centralised audits. This was later extended (at least in intent) to feed and bedding suppliers.

The SoFAQ audit commission recognised that the cost of individual laboratory audits of suppliers was becoming punitive and that the auditees experienced much repetition. The latter were in turn voicing their unease at the apparently contradictory requirements of successive audits performed by different auditors. Both ISO/CEI 25 guidance and ISO 9000 appeared to require supplier audits, as many suppliers who adopted ISO standards as their quality system quickly discovered.

Several meetings were held between SoFAQ and GEFA to agree on how to proceed. Members of both organisations saw that they had a self-interest in going down this path; GEFA was for a harmonised and professional approach to auditing while SoFAQ wanted to highlight inadequacies and wanted to have greater influence in getting things done. Both agreed that, in terms of costs, a reduced use of resources would be desirable.

Three objectives were set for these audits:

- To assess the degree of compliance with national and European legislations on animal experimentation, as applicable to the supplier/breeder (*e.g.* EEC 86/609). In certain cases, US Federal regulations (*e.g.* Endangered Species Act, 1973) were also invoked.
- To evaluate the degree of compliance with the requirements of the end-users, themselves usually regulated by GLP.
- To evaluate the capacity of a supplier to maintain a consistent level of quality in the material supplied.

### 35.1 CONDUCT OF THE AUDIT

The detailed audit guidelines which were developed required the supplier to furnish to the audit team at least the following information:

- Site plan
- Current organisation plan
- CVs and training (past and present) of the personnel
- Job descriptions and responsibilities
- Zoonotic prevention measures employed.

During the visit, the audit team would verify that written SOPs (or equivalents) were present, dealing with such topics as housing conditions, disease prevention, environmental conditions and their regulation, cleaning and disinfection, quality control of water, feed and bedding, quality control of animals, packaging and despatch, *etc.* Transport was seen as a major issue because some suppliers' vehicles stop off overnight during a delivery, and so the places where the animals stayed during the stop became just as important as the places they were bred and housed. Complaints procedures, data recording, storage and retrieval, traceability of individual breeders, health controls and (if relevant) genotyping would also be assessed.

For each breeding type and animal species, the design and housing conditions were assessed. In particular, quarantine capability and pest control were treated in depth. The existence of separate, specialised areas for such tasks as storage of feed and bedding, cleaning of cages and equipment and disposal of carcasses were verified. The environmental conditions were looked at in detail, including the ventilation system and air changes, temperature measurement and control, humidity, light levels and duration, alarm systems and emergency provisions.

In the field of general animal care, the auditors evaluated the veterinary care (and whether this was dispensed by a qualified practitioner), the respect for appropriate ethical and legislative requirements, quarantine procedures, caging types and housing conditions, cleaning procedures, packaging for transport, and behavioural quality and socialisation measures.

Relevant national or international regulatory compliance was verified by reference to legislative authorisation and any animal receipt and delivery registry. Where appropriate, checks were made on the special provisions for dogs, cats and non-human primates, as well as any species protected according to the Washington convention. Animal importers/exporters had their Convention on International Trade in Endangered Species (CITES) permit reviewed.

It is important at this point to state that the audit programme initially agreed upon was emphatically *not* to give certification or accreditation to inspected suppliers. It was to be used to give SoFAQ members preliminary information on which to base an initial judgement on the quality of such suppliers. Thereafter, each laboratory was free to accept the findings of the audit team, or to extend that by performing their own independent assessment. It was considered inappropriate to be



seen in any way to be replacing or invalidating the inspectors of competent authorities regarding animal experimentation.

Having agreed with GEFA on the approach to audits, the audit commission then established an inspection cycle. This was fixed at 10 suppliers per year, audited every 2 years. The commission consulted SoFAQ members every 2 years to ensure that the list of targeted suppliers was still current. Audits were performed by a minimum of two people, one of whom was always a member of the SoFAQ steering committee. Candidate auditors were required to have a minimum of 5 years' experience in quality assurance and to have had some previous experience of auditing suppliers. Each auditor's CV was held by the steering committee. A further guideline was prepared on the format of reports, which served to standardise the approach. Each supplier could request the presence of an independent assessor if desired; such a person could not participate in the audit nor in the preparation of the report.

### 35.2 REPORTING THE AUDIT

The audit report followed the above-mentioned guideline: the content followed the order of items listed in the guidelines for audit conduct, and complied with French Standard NF X 50-136-1 (Guidelines for Quality Systems Audits). The report was descriptive: it carried neither opinion nor judgement. Corrective actions suggested during the audit were also detailed.

Once written, the report was sent to the supplier for comment. It was expected that at least, observations clearly requiring action would be responded to. The supplier was also free to add to, or contest, the content of the report. The report was then sent back to the audit team.

The SoFAQ steering committee then issued the report, having first checked that it complied with the standard format and that all observations had accompanying corrective actions. Each report had a standard title page (see example in Annexe 1) and was signed by the audit team and approved by the SoFAQ committee for distribution.

Reports were made available by subscription. Less frequently used suppliers were, of course, only of interest to the relatively few end-users, so to avoid an imbalance, the popular and less popular were mixed in any audit year, and all the reports for a given year had to be purchased by the subscriber as a package. Subscribers were classed as laboratories having at least one paid-up member of SoFAQ and having paid the annual audit subscription. Reports were sent to the quality assurance department or, by default, to the SoFAQ member concerned. Suppliers also received their own copies of the audit.

### 35.3 CONFIDENTIALITY

Each of the laboratories receiving the audit reports agreed to treat them exactly as they would an internal QA audit, and not reveal the contents to external regulators or clients. To this end, each report was supplied with a separate report statement, which could be used as proof in the event of questions, without revealing details. Distribution of the reports outside the end-user establishment(s) was forbidden. Copying of reports was only permissible if the entire report was involved. Copying or distribution of the report by the supplier was at their discretion. These confidentiality concerns were validated by signed agreements on behalf of the end-users.

Although this chapter has dwelt at length on the centralisation of audits of animal suppliers, the principle can easily be extended to many other areas. Animal feed and bedding suppliers have already been mentioned, but one could also imagine the same approach applied to suppliers of analytical reagents for chemical analysis, chromatography columns, fixatives for necropsy and histology, standard test kits for haematology analysis and so on. Non-GLP analytical laboratories such as those that regularly perform microbiological tests of water quality might also be included.

Each supplier will necessarily require an approach specific to the type of material supplied – what is appropriate to request of a feed supplier would probably not be so in the field of chemical reagents. In order to ensure consistency, it may be useful to adopt a “check-list” approach, with the

proviso that a check list is only a guide, and should not be used as an exclusive means of auditing. An example check list is provided in Annexe 2.

There will inevitably be some difficulties in adopting a centralised approach to auditing suppliers. The availability of competent auditors may, in some countries with small national QA societies, be a limitation. There is then the question of whether, following a somewhat negative audit, a company will elect to sever their relationship with a given supplier.

The positive aspects as revealed by the programme operated in France were that each of the suppliers audited demonstrated a willingness to learn about GLP and change their systems and practices where necessary to become more compliant with their clients' needs. To that extent, the scheme was a tremendous success. The goal of continuous improvement for the better-known suppliers was a catalyst in the development of a trusting relationship. For the smaller, less well-known suppliers, one incentive seemed to be becoming known as a quality supplier in the face of considerable competition from many concurrent businesses. There seemed to be a limitless supply of companies, for example, imagining that it was as easy to produce rabbits for the table as well as for research.

Finally, personal experience has shown that the attributes most required for success in centralising supplier audits are complete agreement on the objectives in advance between the auditor and auditee, an open and flexible approach on the part of auditors and regular liaison between the two parties to ensure that each is providing what the other wants.

In summary, stated below are the authors views on the arguments for and against applying a centralised approach to auditing suppliers.

### **35.3.1 Pitfalls/Difficulties for this Type of Auditing**

- Not always possible to find two societies to represent the interested parties
- An adequate supply of high level/acceptable auditors
- The need for a pre-determined and agreed list of points to be reviewed during audit
- Finding mutually agreeable dates between auditors and auditees for the audit
- Financing the audit. Who pays for the transport costs? Is it legal for an association to reimburse for these and other expenses? What about insurance?
- Preserving independence. Some companies for whom the selected auditors normally were employed seemed to think that the auditors were still working for them and were being paid by them, so those companies thought it was reasonable to expect to receive the report of the audit for free.

### **35.3.2 Advantages of this Type of Auditing**

- Consistency
- Fewer audits, of higher value
- Overall, less disruption and loss of time in performance
- Companies using suppliers get more reports than if they planned the audits as part of their own programme
- Annual meetings between the auditors and auditees help to fix priorities for improvement
- Follow up audits planned as a function of the actions proposed by each audited company.

## **ACKNOWLEDGEMENT**

David Long was among the founders of the centralised supplier audit as operated in France. He corrected some of my misconceptions about the early history of the process and offered valuable additional comments. Alain Piton kindly provided details of the check list used by Pfizer; he and they showed typical willingness to share their experience.

## ANNEXE 1

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### Sample Title Page for Audit Report

#### SUPPLIER AUDITED

(Name, address, telephone & fax numbers)

#### LIST OF ANIMAL SPECIES CONCERNED IN THE AUDIT

#### AUDIT TEAM

(Names, companies, positions or office in SoFAQ)

#### AUDIT CALENDAR

Date(s) of audit:

Date draft report sent:

Date reply received from supplier:

Date of signature by audit team:

Date of approval by SoFAQ committee:

#### REPORT SUMMARY

Title Page

Conduct of audit (including observations)

Audit report

Annexes

Plan of establishment

Corrective action(s) proposed

#### DATE & SIGNATURE OF AUDIT TEAM

#### NAME(S), DATE(S) AND SIGNATURES OF SoFAQ COMMITTEE

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## ANNEXE 2

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### Supplier Audit Check-List

*(This is a general list of elements which it may be important to assess; it should be adapted in each case to the type of supplier audited)*

#### GENERAL ORGANISATION

The establishment must maintain the following documents and make them available to the audit team:

precise, scale plans  
 up to date organisation chart  
 staff CVs and summaries of training, both “on-the-job” and extra-mural  
 job descriptions  
 training plans  
 organisation for the prevention of zoonoses.

#### QUALITY PLANS

Check for the presence of authorised, written operating procedures for the following aspects:

- housing and care of the animals, prevention of diseases
- regulation and control of environment and air-conditioning applicable to each species
- breeding conduct and management
- cleaning and maintenance of materials and facilities and disinfection methods
- water, foodstuff, bedding, and materials quality control
- sanitary (and, if appropriate, genetic) quality control of the animals
- processing of orders
- packaging and expedition
- treatment of complaints
- recording, storage and retrieval of raw data
- provision by management for assurance that these procedures are respected and followed-up
- formalisation of short- and long-term quality objectives (*e.g.* treatment of anomalies, *etc.*).

#### INSTALLATIONS

The audit team will evaluate each of the following items, by breeding type and by animal species:

##### *Design*

access procedures, limits and control

adequacy of facilities for their function

facility maintenance programme.

### *Housing rooms*

floors, walls and ceilings (nature of materials: non-slip, waterproof, smooth, non-absorbent, detergent-, acid-, and solvent-resistant)

ease of cleaning of materials, suitability for chemical disinfection and resistance to high-pressure sprays and normal usage

barriers to keep out insects, wild rodents or other vermin

cohabitation of different species

existence of rooms for isolation and care of animals.

### *Service rooms*

existence of specialised areas:

for receipt and storage of feed according to the manufacturers' instructions;

for receipt and storage of bedding materials;

for storage of clean equipment;

for cleaning and sanitisation of cages and equipment;

for storage and disposal of carcasses;

circulation that assures separation of clean and dirty equipment by time or place.

### *Environment*

separate eating, drinking and smoking areas for personnel

ventilation system, relative air pressures, air changes

systems for control, measure and regulation of room temperature and air-conditioning

regulation and control of relative humidity

lighting, intensity and time controls

noise control

alarms, procedures for surveillance, provisions for emergencies and/or failures (power system, etc.).

### *Animal care*

presence of a qualified person for veterinary care

records of preventive treatment

conditions of packaging for expedition

notification of delivery conditions, respect of ethical rules and compliance with the relevant legal specifications

breeders' requirements for conditions of animal receipt by the end-user

procedures for quarantine and air-conditioning

caging and housing (cage/pen materials, nature of the bedding, cage size, floor area/animal, ethologic needs of each species)

husbandry (feeding and watering procedures and devices, quality control)

exercise of the animals, contact with man or socialisation, behavioural evaluation

cleaning: validity and respect of procedures

documentation and traceability of breeder details.

## **REGULATORY REQUIREMENTS**

The audit team will assess the level of compliance with relevant regulations, particularly with respect to the following items:

proof of establishment authorisation (if needed);

animal receipt register (contents, responsibility and storage);

animal delivery register (contents, responsibility and storage);

(Note: a register may be a computerised system containing all the required information)

special provisions for cats, dogs and non-human primates;

special provisions for protected species according to the Washington convention.

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# Document Control: From Concept to Archiving

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## 36.1 INTRODUCTION

Document control is an essential aspect of any business in today's highly competitive and demanding environment. The constant barrage of customer and business requirements in ensuring goods and services meet the high levels of quality, within tight deadlines, means demands on document control have never been greater in ensuring businesses maintain that important edge over the competition.

Good document control assists businesses to deliver accurate, high-quality services and products efficiently, by ensuring that up-to-date information and requirements are communicated throughout the business quickly and effectively.

All this apart, a business still has to evaluate and address, as applicable, the relevant requirements stipulated by legal and regulatory authorities.

All regulatory authorities regard document control and its preservation as an integral part of compliance with the relevant principles of maintaining good clinical, laboratory and manufacturing practices (GCLMPs). The maintenance of the associated raw data and specimens is the only means to validate and challenge the information produced in the final report.

The guidelines that follow concentrate on the archiving and preservation of raw data based upon good laboratory practice (GLP) principles, and therefore as a rule of thumb, will also satisfy the basic requirements of good clinical and manufacturing practices. It must be remembered that these are only guidelines, the extent to which a business implements mechanisms and allocates resources to maintain document control, must be defined by its management. Individual companies must ensure that they evaluate the business, customer and regulatory requirements in satisfying good clinical, laboratory and manufacturing practices, while balancing commercial considerations against any associated risks.

## 36.2 BASIC PRINCIPLES

The GLP regulatory authorities require that somebody be responsible for the conduct of a study, namely a Study Director. This individual, from the date of signing the study plan, ensures the study follows the plan, documents any deviations from the original plan and issues a final report to finalise the study. They then must ensure it is archived. Exceptions to this order of events include specific studies to be submitted to the US Environmental Protection Agency (EPA) which requires the data to be archived during or at the close of the study. The Study Director must comply with this prior to signing the compliance statement.



It is the responsibility of the Study Director to ensure that the study plan, final report, raw data and supporting material are archived. With the notable exception of the US EPA, other regulatory authorities, such as the Organisation for Economic Co-operation and Development (OECD) and US Food and Drug Administration (FDA), GLP regulations give no specific guidance on timeframes for completing this task. Limited guidance states only that it should be done at the completion of the study and the OECD also state in their advisory document entitled “The role and responsibility of the study director” that this should be done in a “timely manner”. Therefore, Management must define the timeframe within which this task will be performed in its Standard Operating Procedures (SOPs), following evaluation of the business requirements and security risks that exist prior to the secure lodging in archives. Once the data have been transferred to the archive, then responsibility for its safekeeping is transferred to management.

It is management’s responsibility to ensure that archive facilities are provided, and that a person is identified as responsible for the management of the archive facilities. Often, this individual is identified with the job title of “Archivist”, although other job titles may be used. The Archivist becomes custodian of the materials they have been given on behalf of management and they must inform management of any issues or deviations from the company policies in ensuring the preservation of the material in their care.

It should also be remembered that non-study-specific information must also be maintained, *e.g.* SOPs, maintenance logs and staff training files, as the inspecting regulating bodies will also wish to inspect these records.

The following sections of this chapter highlight areas for consideration when addressing requirements for archive storage, but it should be remembered that these are for guidance only and management must evaluate their own changing business needs as well as current regulatory requirements.

### 36.3 FACILITY

Regulations specify that the archive facility should provide secure storage for materials and the design and conditions should protect the contents from untimely deterioration. This is a very vague statement in the broadest terms. Archive facilities can range from a locked office filing cabinet to entire buildings built for archiving.

Whatever the size or shape, management must ensure that the facilities are “fit for the purpose”. In other words, ensure that adequate archive facilities are available for the current and future business needs.

It should be made of good solid material designed to withstand the elements of local weather conditions and ideally built in a location that is not susceptible to flooding or earthquakes. It must be located and built to conform to local building regulations.

Basement locations or installation of central heating systems and running water pipes in or around the archive areas should be avoided considering the risks associated with flooding.

The facility must be secure to prevent unauthorised access to the data and be designed to prevent unlawful entry. This may involve the installation of deterrents in the form of security guards, CCTV, re-enforced doors and alarm systems to discourage unauthorised entry to the facility; alternatively, just a good lock could well be enough for the purpose.

Access restrictions also cover unauthorised access by the company’s own employees. At the very least, individuals should sign into the facility, to leave documented evidence that they have been granted access. Consideration should be given to installing a combination of secure locks or an electronic card entry systems, which manage this more effectively.

The facility should as far as possible be fireproof and conform to local regulations regarding fire prevention. Any use of naked flames, or other open heat source should be prohibited, and

appropriate safety checks should be performed on electrical equipment and circuitry within or around the archive.

Smoke alarms and fire detection systems must be installed. For a basic means to fire-fighting, fire extinguishers should be readily available, preferably those which use carbon dioxide or the other non-aqueous types. The local fire department will be a good first choice in assisting with selecting the correct types of extinguishers needed and advice on fire prevention.

Installing automated fire suppression systems should also be considered. With recent advances in freeze–vacuum drying techniques, even water suppression systems can now be considered; after all, having something to recover may be better than having nothing at all!

As a part of the company's Business Continuity Assessment, consideration should be given to subscribing to organisations that specialise in drying and restoration techniques, which should become part of the disaster recovery programme. These organisations have a wealth of knowledge, experience and facilities/equipment to assist in the recovery of data.

Extreme variations of temperature and humidity must be avoided as this may contribute to the deterioration of the materials being stored. Installing a system to control the environmental conditions in the archive automatically is advisable. Air conditioning is the best means to control this, ideally with the electrical unit located outside and separate from the facility as this will reduce any potential risk of fire if the unit fails.

The use of windows in the archive areas should be restricted as direct sunlight may also damage the materials stored there. The facility should as far as possible protect the material from rodent and insect pests, as any infestation may cause damage, and accordingly it is recommended that the archive areas operate effective pest control procedures.

Installing mobile racks should be considered as it ensures the most efficient use of space; however, it may also cause structural problems due to the uneven distribution of weight in archive areas not situated at ground level. Metallic shelving is the most versatile shelving for an archive as other materials may require treatment, which in itself may affect the materials being stored.

Procedures should also be in place to monitor the capacity of the facility, so that the archivist can give the management advance notification on the capacity of the archive and any potential requirement for new facilities. This monitoring of future requirements, however, is not at all a one-way traffic. Feedback from management is also needed to inform the archivist of future business development plans, so forecasts on potential requirements can be calculated, thus ensuring that the business is managed in a pro-active way.

Depending on the size of the organisation, management may feel that the building of an archive facility may be a drain on the company's capital resources and may opt to contract this service to a commercial archive. With the exception of studies that will certainly be submitted to Japan's MAFF regulators, who state materials should be retained at the testing facility at which they were generated, no mention is made in any other regulation stipulating that this is a mandatory requirement. The Archivist should maintain records of any material stored and its location.

As the company is responsible for ensuring that the data are maintained in accordance with the relevant regulations, any facility selected to provide archive services should be regularly audited to ensure that they maintain compliance with the relevant current regulations and contractual agreements.

### **36.4 STAFF COMPETENCY**

Regulations do not stipulate specific or special qualifications for the role of an Archivist. They expect an Archivist to be competent in the role as much as any other individual involved in the conduct of a GXP study. So the management can now decide the criteria that the individual should meet to fulfil the job expectations.

Experience or qualifications in record management or similar vocations would be desirable but is not a requirement as routinely the individual may come from other fields, bringing previous training and experience into the role. A good understanding of the relevant regulations would always, of course, be advantageous.

Dependent on the size of the operation and business requirement, the Archivist may need to delegate duties to other responsible individuals working within the archive. Indeed, a deputy should be identified in order to provide cover for the Archivist during any periods of absence. In larger facilities, where a team of archive staff is managed, the Archivist will typically possess good management skills in order to ensure they delegate responsibilities effectively while maintaining regulatory compliance. The Archivist's assistants will also require relevant training so as to be able to assist the Archivist in their responsibilities.

Staff training files, containing job descriptions detailing responsibilities and curriculum vitae summarising relevant training should be maintained for all archive personnel, providing evidence of the level of competency achieved.

It should be remembered that management should always provide training specific to their business requirements. Further assistance can be gained from associations such as the UK Scientific Archivist Group. This group has been established for over 25 years, bringing together others working in the field. The spring and autumn conferences the group holds allow valuable networking with other individuals who have a wealth of experience in archiving and gladly offer assistance to other members.

### 36.5 DOCUMENTATION

Management must have clear policies in place regarding their intentions for archived material, which should be approved, signed and dated by senior management. The policies should detail the materials that should be placed in the archives, the timeframe from study completion that material should be placed in the archives and details of required retention schedules should be clear.

Its policies should also detail the expectations and procedures surrounding the requirements for archiving materials, the procedures for access and removal of material from the archive and final procedures for the disposition of materials. The archive facility, like all other operating areas involved in the conduct of the study, must maintain SOPs covering all aspects of the processes within the archive facility. These should be signed and approved by operational management and be periodically reviewed and updated to ensure they remain current to the routine practices and procedures being used.

SOPs should at least provide instructions on the following:

- (i) Definition and description of the facilities which constitute the archive, its security measures including access controls, pest controls, environmental conditions and the materials retained.
- (ii) The procedures for receipt and indexing of materials in the archive.
- (iii) The procedure relating to release materials from the archive and the process of tracking the material while outside the security of the archive.
- (iv) The requirements and procedures governing the final disposition of the material once the retention period expires.

Management of the archive would be advised to give consideration to producing a Business Continuity Plan (disaster plan). It has been proven that archives that have clear, documented procedures that detail the steps to be taken in the event of a disaster in the archive, have a better percentage of recovery of material than those that do not. A good plan will also provide advice on what actions to take to minimise further disruption to the business.

It must be remembered that any plan must ensure that it takes into account the role of the emergency services, as access to the archive for employees will be denied while there is a risk to their health and safety.

### 36.6 TYPES OF RECORDS TO BE RETAINED AND RETENTION SCHEDULES

Some GLP and GCP regulatory authorities give some guidance on what materials they expect to be retained and for how long. It must be remembered that these recommendations from the regulatory authorities are about the minimum retention times whereas businesses may, and often, do adopt policies of retaining records for much longer periods. The OECD guidelines mention that records should be retained for the period specified by the appropriate authorities. Therefore, the assumption that can be derived from this is that this will be the appropriate licensing for the regulatory authority within the country in which the product is intended to be marketed. There may also be implications if the product is subsequently marketed in other countries as well, since the material may then be required for a period longer than the original licensing or regulatory authority expectations. It must also be remembered that after the license has been granted, the licensing authority may formally request further information. If the data is not available to reconstruct a study, then the licensing authority may decide to disregard that data, thus in effect calling the whole license system into question. The sensible advice, therefore, offered to companies is that it may be advisable to retain the data for the time that the product is in the market, as for as long as there is a possible regulatory question to answer.

This is fine for products that reach the market successfully. However, for compounds that are not successful, some regulations state that these records should still be retained for a minimum period. The probable reasoning behind this is to allow the regulator's time to audit the material as part of their compliance monitoring programme. Regarding the retention of samples and specimens, all the regulations require that these should be retained only till their quality allows a valid scientific evaluation of them. Because of this, wet specimens of blood, urine, faeces and biological fluids would not routinely require retention. There should be no problems in routinely retaining fixed wet tissues for the minimum periods specified in the relevant regulations.

Other records should also be maintained to support the study-specific data and assist in the reconstruction of the study if necessary. Records such as retention schedules, equipment and calibration checks, Quality Assurance records, a historical file of SOPs, staff training records and job descriptions, master schedule records, computer validation documentation and environmental monitoring records should also be maintained in the archive.

All such supporting records should be preserved for at least the same periods specified for study materials, but in reality may be required to be maintained much longer as these types of records may apply to multiple studies. They may also need to be retained for longer periods to satisfy other legislations; for example, the rule in the UK COSHH is that records there must be retained for at least 40 years. However, the format in which these records are maintained is not specified, as the regulations only state that a record should be maintained. Therefore, it is possible to interpret that this information may be stored on microfilm or in electronic form as long as the procedure is fully validated, thus making it possible to reduce the volume that this material occupies in the archive. It is advisable for management to gain guidance from their local regulatory monitoring authority on the acceptability of any proposed approach before disposing of any original record.

Table 1 details the minimum expectations of some of the regulators. However, this is a summary of the possible regulations that may be relevant when evaluating retention requirements. It should not be used as the sole reference for such retention decisions. Before any disposition of materials are decided upon, companies should refer to current regulations and monitor application activities to ensure that both the full range of regulatory requirements and the potential business needs are satisfied.

**Table 1** *Guide to good laboratory and clinical practices minimum retention requirements (reference should be made to current regulations)*

<i>Authority</i>	<i>Regulation</i>	<i>Raw data requirements</i>	<i>Specimens</i>	<i>Country</i>
Organisation for economic co-operation and development (OECD)	Principles on Good Laboratory Practice ENV/MC/CHEM(98)17 (Revised in 1997, issued January 1998)	For the period specified by the appropriate authority	Same as raw data  Samples should be retained for as long as the quality allows evaluation	Various
Medicines and Healthcare products Regulatory Agency (MHRA)	Good Laboratory Practice Regulations 1999, Statutory Instrument, 1999 No. 3106	For the period specified by the appropriate authority	Same as raw data  Samples should be retained for as long as the quality allows evaluation	UK
Federal Drugs Administration (FDA)	Good Laboratory Practice Regulations for Non Clinical Laboratory Studies (ISSUED 22 December 1978 Federal Register Plus subsequent amendments)	( <i>Whichever is shortest</i> ) At least 2 years following completion, termination or discontinuation of the study  At least 2 years following the date of permit approval by the FDA  At least 5 years following the date on which the results are submitted to the FDA in support of an application permit	Same as raw data  Samples that differ in stability should only be retained for as long as the quality allows evaluation	USA
Environmental Protection Agency (EPA)	Toxic Substance Control Act (TSCA) Good Laboratory Practice Standards (Issued 29 November 1983 Federal Register Plus subsequent amendments)	At least 10 years following the effective date of the applicable final test rule	Same as raw data	USA

**Table 1** (Continued)

<i>Authority</i>	<i>Regulation</i>	<i>Raw data requirements</i>	<i>Specimens</i>	<i>Country</i>
		At least 10 years following the publication date of the acceptance of negotiated test agreement	Samples that differ in stability should only be retained for as long as the quality allows evaluation	
		For testing submitted under Section 5 of the regulations, materials should be retained for 5 years following submission of the results of the study to the EPA		
Environmental Protection Agency (EPA)	Rodenticide Act (FIFRA). Good Laboratory Practice Standards (Issued 29 November 1983 Federal Register Plus subsequent amendments)	( <i>Whichever is longest</i> ) For the period during which the sponsor holds a permit approved by the EPA	Same as raw data	USA
		At least 5 years following the submission of study results in support of an application for a permit	Samples that differ in stability should only be retained for as long as the quality allows evaluation	
		At least 2 years following completion, termination or discontinuation of the study		
Ministry of Economy, Trade & Industry (METI) (Previously Ministry of trade and industry (MITI))	Good Laboratory Practice Standards for Agricultural Chemicals 11 Nousan-No. 6283, 1 October 1999	A period of 10 years after receipt of notice	Either 10 years after receipt of notice or the period for which stable storage is possible, whichever is shorter	Japan
Ministry of Health, Labour & Welfare (MHLW)	Good Laboratory Practice Standards for non-clinical Safety Studies on Drugs (GLP) Ordinance No. 21	5 years from the date of application approval	Same as raw data except for materials recognised by its nature as difficult to preserve	Japan

(Continued)

**Table 1** (Continued)

<i>Authority</i>	<i>Regulation</i>	<i>Raw data requirements</i>	<i>Specimens</i>	<i>Country</i>
		5 years from the date of completion of re-examination 5 years after reporting of data used as grounds for adverse reaction		
Ministry of Agriculture, Forestry and Fisheries, Japan (MAFF)	Good Laboratory Practice Standards for Agriculture Chemicals 11-Nousan-No. 6283, 1 October 1999	15 years at the test facility after the first registration of chemicals relevant to the study	Specimens and samples of test and reference items should be retained for a period of at least 5 years after the first registration of chemicals relevant to the study The above should only be retained for as long as the quality of the preparation permits evaluation	Japan
Medicines and Healthcare products Regulatory Agency (MHRA)	'The Medicines for Human Use (Clinical Trials) Regulations 2004' (SI 2004 No. 1031)	Essential documents should be retained until at least 2 years after the last approval of a market application and until there are no pending or contemplated market applications Essential data from trials that are not to be used in regulatory submissions should be kept for at least 5 years after completion of the trial. These documents should be maintained if required by Sponsor or other applicable regulatory requirements		UK
ICH Harmonised Tripartite Guideline	Good Clinical Practice	Essential documents should be retained until at least 2 years after the last approval of a market		



**Table 1** (Continued)

<i>Authority</i>	<i>Regulation</i>	<i>Raw data requirements</i>	<i>Specimens</i>	<i>Country</i>
		<p>application and until there are no pending or contemplated market applications</p> <p>At least 2 years have elapsed since the formal discontinuation of clinical development of the investigated product</p> <p>They should also be kept for a longer period if required by the applicable regulatory authority</p>		

### 36.7 INDEXING

The regulations state the materials maintained in the archive must be indexed. Words like “expedite” and “facilitate orderly storage and retrieval” are mentioned but really do not give much assistance in evaluating how much detail goes into the indexing process. The level of indexing is, therefore, left to management of the facility to ensure that the system they use will provide retrieval of the material in a timely manner, while at the same time satisfying their own business requirements.

The indexing system for archived material is one of the most important aspects of the function. It is a basic fundamental requirement of any archive to know what material is being stored and its location. Having poor systems will lead to materials being misplaced or worse – the realisation of every Archivist’s worst nightmare – losing the records. The procedure for indexing and tracking materials does not have to be a complicated one. A simple card system may suffice, though realistically a computerised system offers the most versatile method of indexing.

Computer systems allow rapid retrieval of multiple studies from various locations, can assist in the cross-checking of materials, and allow information to be sorted, processed in a rapid, accurate and efficient way. Computer systems can also be integrated to provide management information on the capacity of the facility and projected fill rates to assist in managing archive resources.

Systems incorporating the use of barcodes also have many benefits. Barcode systems facilitate rapid identification of the materials allowing the archive process to be more efficient. They can also provide the valuable benefit of reducing the potential risk of misplacing material in the archive due to human error!

The use of computerised systems now brings with it additional responsibilities in that the management must follow the regulatory guidelines associated with the use of such systems. Computerised systems should be suitable for the intended purpose, validated, operated and maintained as defined under the relevant regulations. This can place significant demands on resources, depending on the complexity and size of the system, and there are further associated costs in keeping abreast of future software upgrades, maintenance contracts, system support contracts and training. Management must provide the necessary resources if computer systems are to be used.

It is often apparent that some people expect the Archivist to index material. True, the Archivist must ensure that any material archived is indexed. However, many archives are a central repository for information from many different “specialist” fields. Therefore the expectation that an Archivist should have the knowledge and understanding of all material they handle is unrealistic. The indexing

process is best incorporated into the procedure of submitting the data to the archives. Typically, there would be a process of documenting on a check list the material that is to be archived. This enables the Study Director or their responsible delegates to list the material they want to archive and review the list to ensure that the materials to be submitted to the archive have been submitted. As it is the Study Director's legal responsibility to ensure the study materials are archived, then this checklist will provide documented evidence that these requirements have been completed.

The checklist should be presented with the data to the archive personnel, who should use it to check that all the material that has been identified on the checklist is accounted for. There should also be provision on the form to allow all parties involved to sign the form, once they are satisfied with the form-content. This will provide documented evidence that the transfer of responsibility for the listed material has changed from the Study Director to management, thereby providing a trail of accountability for regulatory purposes. This process should also be used for the archiving of non-study-specific data that is required to be maintained in support of study-specific materials submitted by operational areas. Once in the archive, completed checklists can be used by the Archivist as the basis for the index of material being stored.

It is advisable that other information is also entered on the indexing systems maintained in the archive. In order to facilitate searches of the index, it is recommended that it should hold information on the test compound (*i.e.* its identity), the Study Director, study type, final report date, retention review date and other information dependent on business requirements. In doing this, a good indexing system can also be a good management tool. It will not only allow the Archivist to manage future enquiries more efficiently and assist in the process of deciding the final disposition of material after the retention period has expired. It can also be customised to assist in the monitoring of fill rates of the facility, as this is essential to evaluating future archive resource requirements.

### 36.8 RESTRICTIONS

Although the regulations state that only authorised persons can access the archive, it is left to the management to define who has access and the restrictions they consider appropriate.

It makes good business sense, that only the people that management identified as responsible for assisting in facilitating the management of the archive function should have access to the archives. After all, as the custodians of the material, having been charged with the responsibility for its preservation and safekeeping, they would probably be held accountable by management if things went wrong!

In realistic terms, with all but the most basic of indexing system, individuals unfamiliar or untrained in the use of the system would struggle to find the information they were looking for. Granting access to non-archive staff will only increase the potential risk of misplacement or damage to the archived materials.

Visitors to the facility should always be accompanied by one of those individuals who have been granted access by management who must ensure that no material is misplaced or tampered with. A log of visitors to the facility should be maintained to show who has been granted access into the facility.

In addition to restricting facility access, management must also restrict access to the data. Remember, once the study has been completed and transferred to archives, its maintenance and preservation becomes management's responsibility. It is important to ensure that these individuals who generated original data cannot subsequently amend the data after audit/sign-off.

In the interest of the archived material's safekeeping and preservation, the handling of archived materials should be kept to a minimum. Most of the information to satisfy queries should be found in the study's final report. In the event that further clarification is needed, then access to the data should still be granted only as a last resort.

If provisions for microfilming or scanning data into electronic form have been applied, then this must be used in the first instance. Only in the event that the image captured is not readable, for whatever reason, should access to the actual data be sought. However, in the event that access to the data is required, procedures, in the form of company policies and SOPs, should be in place to deal with such eventualities. These should detail the circumstances that access to the data is permitted, define the management personnel who have the authority to permit removal of material from the archive facility, and the tracking procedure for monitoring the data while outside the security of the archive. On return to the archive, the material should be thoroughly checked to ensure that it is complete and management is informed of any discrepancies.

The documentation used in this process showing the authorisation and reason for access should be retained with the study data, to record the events that occurred. Ideally, a room in the archive facility, but away from the main archive area, should be provided to allow such reviews of study material to be performed *in situ*. Removal of specimens from the archive should follow the same procedures. The new slides or data that are generated should be archived and indexed with the rest of the study material, along with any amendments to the final report.

## 36.9 STORAGE CONDITIONS

Most guidance dealing with storage of archived materials is aimed at the material's preservation long after any of the times most regulations require. Such guidance is mainly aimed at establishments such as museums, public record archives, libraries and Government archives, which require the records to be preserved for the historical value and potentially for an indefinite period. An example being BS 5454: Storage and Exhibition of Archival Documents.

These standards do provide valuable guidance on the recommended storage conditions for different materials and explain the rationale for such standards. Nevertheless, these are guidelines, not legal requirements, and the responsibility of how much resource is provided and to what extent it is applied for study material preservation is left in the hands of individual company management.

The GxP regulations make no statements about which standard or parameters should be followed in ensuring the preservation of archived materials. However, although under the regulations there is no requirement for the environmental conditions to be monitored, it is recognised by industry and standards such as BS 5454 that effective preservation of the material requires the control of the environmental conditions. It should be noted that if environmental conditions are monitored and the procedures are detailed in an SOP, then the regulators will audit the procedures and parameters the company has set themselves as part of their monitoring compliance programme.

If the facilities mentioned in the foregoing are provided, it should be adequate for the Archivist to manage the storage and preservation of most records generated from GLP, GCP and GMP studies. Therefore, once they have evaluated their own business requirements, they may wish to use the information in the standards as a guide to setting their own working parameters.

### 36.9.1 Paper

Records on paper are still the most common medium used for recording information. Although more and more records are being captured in electronic form, paper records require no special skills in its handling/processing and its content can be interpreted/transported easily in the ever increasing "Global" business environment.

Paper comes in various shapes and sizes, which in itself should provide no problems to the Archivist in its preservation. Nevertheless, the Archivist should be aware of the use of continuous or perforated form of paper, as it is best to ensure that when operations are required to use such papers, it remains as one continuous sheet ensuring the record remains intact.

Routinely, the chemical composition of the materials used to produce the paper will be of more concern to the Archivist in ensuring the record's continued conservation. Paper records may be presented for archiving which have used thermal or impact-sensitive paper or may have information recorded using non-permanent ink. These records should be copied as soon as possible as deterioration is inevitable in a short span of time. Companies may wish to restrict the use of such material if possible.

Environmental conditions do affect the long-term storage of paper documents. Too dry an atmosphere and it becomes brittle, too moist and it may encourage mould growth. Excessive heat may also accelerate potential chemical damage.

The environmental conditions should, therefore, be controlled to ensure that there are no large or sudden fluctuations in temperature or humidity. A temperature range of 15–25 °C and relative humidity range of 40–65% should ensure that most material's life expectancy will meet relevant regulatory requirements. However, individual companies may decide to set different parameters, such as those detailed in documents such as BS 5454, when they evaluate their own requirements.

### 36.9.2 Electronic Media

With advancement in e-records, more and more information is being captured in an electronic format. Electronic records usually require special training as well as access to relevant hardware and software to be read by the human eye. This in itself causes further problems to the Archivist in the fact that specialist training may be required to maintain and understand the material being archived.

With continued advancements in computer hardware and software, the amount of systems the archivist would need to understand could become unmanageable. The sturdiness and lifespan of the media on which these electronic records are captured are also continuously being upgraded as manufacturers strive to ensure that their products are the best in the market.

Operating platforms are being upgraded/changed more frequently too, as IT policies of the company are constantly being reviewed to ensure harmonisation in the "Global" environment. These changes are usually out of the hands of the Archivist.

It is advisable that the above issues should be addressed in the validation procedures of any computer system. Guidance in validating computer systems can be found in the OECD Consensus document for 'The Application of the Principles of GLP to Computerised Systems' and companies should also review US FDA CFR 21 Part 11 Electronic Records; Electronic Signatures; Final Rule.

It may be decided by management that dealing with data stored on electronic media and the preservation of the storage media is the responsibility of the company's Information Technology Department or other such specialist bodies within the company. After all, they will probably have training and knowledge of the systems installed within the company and will be aware of any impending changes, the reason for change, and any problem the change will have on current systems.

Access to this data must still be restricted, controlled by the Archivist and follow the procedures that have been implemented for other materials stored in the archive.

Any duplication, back-up, transfer of data to another system or final disposition should be clearly documented to record the events that occurred.

This should be clearly documented in either the company's policies or SOPs to clearly differentiate the responsibilities between the Archivist and any other involved personnel.

The environmental conditions specified above for paper may be acceptable for the preservation of some forms of electronic media being retained for the minimum periods specified in the relevant regulations. However, after evaluation of their own systems, companies may wish to provide facilities that control environmental conditions specific to their own requirements and with tighter controls to ensure that data maintained in an electronic format is preserved to ensure compliance with the regulations mentioned above. Further, assistance in setting parameters of environmental

conditions and in preserving electronic media can be found in BS 4783:1- 8: Storage, transportation and maintenance of media for use in data processing and information storage. Guidance should also be sought from the relevant product manufacturers.

### **36.9.3 Specimens**

As mentioned previously, all the regulations require that samples and specimens should be maintained for as long as their quality allows a valid scientific evaluation. Because of this, wet specimens of blood, urine, faeces and biological fluids would not routinely require retention.

Wet tissues fixed in formalin solution should pose no problems routinely being retained for the minimum periods specified in the relevant regulations. If checks are performed on such materials and they are found to be no longer viable, this should be validated by a pathologist or other suitably competent person, then these specimens may not routinely be required to be retained further. Details of the disposal of such materials should be maintained in the archives until such time as it is decided that the other study data can also be disposed of.

Organs and tissues set in paraffin blocks or set onto slides can be retained for many years if stored in facilities of the type specified earlier in this chapter. All of these types of biological specimens require no particular controls on environmental conditions other than common sense in ensuring that they are not exposed to extremes of temperature or humidity.

Health and Safety precautions regarding the handling of such materials and exposure to chemical fumes must be evaluated to ensure minimal risks to employees. After evaluation, relevant protective equipment and ventilation systems may be required to be provided.

Check lists should be used for specimens, as with other materials, showing the details of what specimens have been lodged in the archive.

## **36.10 CHALLENGES AHEAD**

It is likely that for the foreseeable future, regulatory requirements will continue to require the retention of wet tissues, paraffin blocks and glass specimens. Although more and more information is being generated and stored in electronic forms, the paperless archive still seems to be a long way away. Humans are used to handling paper and reading it. It provides them a sense of comfort, as shown by many of us who still print an electronic document to ensure we have understood its content correctly!

Paper also provides a sense of security to people as they know that the information upon the paper will still be able to be evaluated in many years to come without the need of further resource. How many of us are sure that the same can be said for electronic data? Whether a company switches from paper archives to electronic data stores, the need for good document control remains the same so as to ensure compliance with the current regulations and maintain an effective business.

One thing is for sure: in these exciting times the Archivist's role will continue to be a varied and demanding one, add to this the uncertainty of what issues they will encounter next in the world of records management and archiving!

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Part 3 Recommendations for flexible disk cartridges;  
 Part 4 Recommendations for magnetic tape cartridges and cassettes;  
 Part 5 Recommendations for 12.7 mm magnetic tape cartridges for data interchange, recording at 1491 data bytes per millimetre on 18 tracks;  
 Part 6 Recommendations for optical disk cartridges (ODC);  
 Part 7 Recommendations for optical data disks (CD-ROM);  
 Part 8 Recommendations for 4 mm and 8 mm helical scan tape cartridges;

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## OTHER USEFUL READING MATERIAL

“Medicines and Health Care Products Regulatory Agency: Good Laboratory Practice Guidance on Archiving”, March 2006.



## CHAPTER 37

# Computing and GXPs

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### 37.1 INTRODUCTION

The use of computer technology within the GXP environment has been a cause of some debate for many years. The vast majority of safety data is now processed by computer systems, and computing technology is at the heart of most manufacturing and drug distribution processes. Medical devices often have an embedded microprocessor that is programmable. Ensuring that a computerised system is ‘fit for purpose’ is, therefore, essential.

Good practice regulations help by providing a basic quality framework that we can build on. However, they do not provide us with a recipe for success – that we have to find for ourselves. There are, of course, a large number of very useful guidance documents on the different aspects of successful systems, and in this short chapter it would be impossible to do justice to this topic by addressing each point in depth. Instead, I have chosen to provide some background to where we find ourselves today and have selected what I believe are some of the major issues that need to be addressed.

If this topic is new to you then you may find the background interesting. Before preparing this chapter, I had not really appreciated just how much GMP thinking had impacted on the GLP/GCP arena – particularly in the validation of systems. Since my own background is in GLP systems, I had assumed that we had started with a clean sheet in the late 1980s but that was clearly not the case. I had also failed to recognise that the evolution of validation under GLP had caused problems in the GMP arena, although I had realised that it was the GMPs that now appear to be setting the pace with a risk-based approach.

All this will be discussed here. It is, of course, my view of what is still a relatively short history and although much of it is objective, I have added my own comments where I felt they could be useful. Similarly, the views I have expressed on individual issues are my own. I would, however, wish to thank the large number of my colleagues who have helped me form these views over the past 30 years or so.



## 37.2 BACKGROUND

### 37.2.1 ‘Validation’ Becomes Essential

During the late 1970s, there was a strong focus within the regulatory agencies and particularly the FDA on ‘validating’ computerised systems<sup>†</sup> used in manufacturing. The intention was to ensure product quality by ensuring that processes were robust, repeatable and under control (Figure 1). The 1983, FDA ‘Guide to Inspection of Computerized Systems in Drug Processing’<sup>1</sup> (often called ‘the Blue Book’) covered the validation of both computer hardware and computer software and provided the following definition: ‘Validation is the assurance, through testing, that hardware or software produces specified and predictable output for any given input’.

The concept that computer systems used in a regulated environment should be validated was extended to cover pre-clinical systems and validation became a major topic during the FDA-sponsored ‘Red Apple’ workshop in 1987. With a mixture of representatives from FDA, industry and academia, the objective was to write a book on what were generally agreed to be the ‘best practices’ at that time. The workshop took place at the Red Apple Conference Centre near Little Rock in Arkansas – hence the name. Although a further workshop and a good deal of editing was subsequently required, the book ‘Computerized Data Systems for Non-Clinical Safety Assessment – Current Concepts and Quality Assurance’ was finally published by the Drug Information Association in September 1988.<sup>2</sup>

One of the key points debated during these workshops was whether the scope of the term ‘Validation’ should be extended to include all the checks that would be carried out during the development of a computer system. From an IT perspective, validation was already well established at that time since it was considered essential for all ‘mission critical’ systems. The Red Apple book therefore defines validation as ‘the process of evaluating a system at the end of the system development process to assure compliance with user requirements’. It also defines the checks that are performed during systems development as verification. This is consistent with the ANSI/IEEE definitions of these terms. In reality, as the chapter on ‘Validation and Verification’ in the Red

- Title/number
- Purpose/objectives
- System description
- Test environment/exclusions
- Test procedures
- Time plan
- Personnel/responsibilities
- Test data:            expected results, error resolution
- Acceptance criteria
- Results/report
- Quality assurance involvement
- Record retention

**Figure 1** *Validation protocol or plan*

<sup>†</sup>When we talk about computer systems, we are usually talking about the hardware and software that are the fundamental components of the system; whereas when we talk about ‘computerised systems’ we include all the associated elements, including infrastructure, networks, equipment and people, who contribute to making the computer system effective.

Apple book states – both have to be taken into account in order to ensure that a system is ‘fit for purpose’.

### 37.2.2 ‘Fit for Purpose’

The Red Apple book attempted to cover all aspects of the development and use of computer systems but not every aspect was treated to the same depth as validation. The book was not a regulatory guideline and was not officially endorsed by the FDA – unlike the Blue Book. Nevertheless, it carried weight with industry and established a precedent where the FDA was perceived as having endorsed a guideline even if it was written with outside help.

Other regulatory agencies produced their own guidance documents. The US EPA produced the first draft of their good automated laboratory practice guidelines in 1989 and the UK Department of Health published their guide on ‘The Application of GLP Principles to Computer Systems’ at the same time.

In 1992, the OECD (Organisation for Economic Co-operation and Development) convened a workshop in Interlaken, Switzerland to find a harmonised approach to the application of GLP principles to computer systems. The OECD view certain regulations as a potential barrier to trade and, therefore, to economic performance of member countries. The GLP regulations had been a focus of attention for OECD from the early 1980s since the mutual acceptance of data from studies conducted in one member country could reduce the delay in the introduction of a new and beneficial drug in other member countries.

As was the case with the Red Apple workshop, a further meeting and much editorial work was required before the OECD consensus document<sup>3</sup> was published in 1995.

The OECD consensus document did attempt to cover the wider issues with the use of computer systems, such as the responsibilities of management, and also attempted to give practical guidance that was not proscriptive. The OECD guideline overlapped considerably with the updated UK DoH guideline and the latter was subsequently withdrawn.

At about the same time that OECD was devising their guidelines for GLP, other industry associations were considering how best to comply with the regulations. One of these groups, ISPE – the International Society for Pharmaceutical Engineers – was working on an initiative to define good automated manufacturing practice (GAMP). The initiative grew out of a recognition in 1991 that the validation of automated systems in pharmaceutical manufacturing had assumed a much greater importance than had previously been the case. The GAMP forum website explains the situation:

*Although regulatory guidelines concerning the use of such automated systems had been available for some time, these systems had been subjected to less regulatory scrutiny than some other areas, and the interpretation of the regulatory guidance was less mature than in more conventional areas.*

*With the increased penetration into, and complexity of automated systems in pharmaceutical manufacturing, the focus on such systems has increased. With it comes the need to improve understanding of the regulations and their interpretation. Better communication is required, not only within the pharmaceutical industry, but also with its suppliers. Thus an informal group, the UK Pharmaceutical Industry Computer Systems Validation Forum (now known as the GAMP Forum) was set up to promote that understanding.*

The GAMP Forum was very successful and attracted membership from around the world, including representatives from the regulatory agencies. The group also included suppliers, and the GAMP3 guide (published in 1998) is now widely viewed as the definitive guidance for suppliers of automated systems to the pharmaceutical industry. The latest version of the GAMP documents, GAMP4,<sup>4</sup> was issued in 2001 and was intended to cover GLP and GCP applications as well as GMP.

### 37.3 THE ELECTRONIC RECORDS; ELECTRONIC SIGNATURES RULE (21 CFR PART 11)

While the GAMP Forum was considering how to comply with GMP, the FDA announced (in 1991) their intention to produce rules that would allow 'electronic signatures' to be used. Initially this was requested by industry to allow batch records required during manufacturing to be signed online. The FDA soon realised that it was not possible to have an electronic signatures rule without clarifying the requirements for electronic records. The birth of '21 CFR Part 11: Electronic Records; Electronic Signatures; Final Rule'<sup>5</sup> took a further 6 years and involved significant input from industry. The scope of the rule was extended to cover all FDA program areas, not just GMP, and because of the extensive debate and the long gestation period, very little time was allowed between the publication of the rule in March 1997 and its coming into effect on 20 August 1997. Part 11 was intended '*to permit the widest possible use of electronic technology, compatible with FDA's responsibility to promote and protect public health*'. It was clearly intended to be enabling legislation, clarifying what was required for good electronic record keeping and allowing for the use of electronic signatures where necessary.

To an industry already struggling with Y2K issues, the perceived additional regulation coupled with the short time between announcement and enforcement caused consternation. There was also concern that the FDA would enforce the rule on pre-existing systems and would not allow hybrid systems, which used a mixture of electronic records being printed on paper and signed by hand. There was also concern that the scope of the rule might mean it could be applied to more systems than had previously been the case.

The FDA adopted a 'collegiate' approach with industry and undertook to provide further guidance on certain key aspects of the rule. In 1999, the FDA produced a draft guidance document on the application of the rule to clinical studies<sup>6</sup> and additional draft guidance documents were produced covering validation, time stamps and the copying and maintenance of electronic records as well as a glossary of terms.

However, the debate continued with a number of bodies that represented industry continuing to lobby the FDA to adopt a more reasonable approach. Despite the fact that the FDA guidance documents were clearly marked on the top of each page with '*Guidance for Industry – Not for Implementation*', they were often treated as regulations. To some extent, they also tended to encourage debate over minutiae rather than the more important issues.

#### 37.3.1 Introducing a Risk-Based Approach

In 2001, the FDA announced a new initiative to '*modernise the agency's regulation of pharmaceutical manufacturing and product quality*'. The ISPE responded by submitting a white paper to the FDA outlining a 'risk-based' approach to the application of Part 11.<sup>7</sup> In August 2002, FDA announced that they would adopt a risk-based approach to the modernisation of the cGMPs.<sup>8</sup>

On 20 February 2003, the FDA issued a press release stating that the first stage of this modernisation had been completed. The press release confirmed that the FDA would focus its attention and resources '*on the areas of greatest risk, with the goal of encouraging innovation that maximises public health protection and promotion*'.

The press release highlighted elements of the initiative that had been completed, including the following:

- '*Clarifying the scope of FDA's electronic submission and record keeping requirements and providing for enforcement discretion in certain areas while FDA considers whether to revise the Part 11 regulations to facilitate innovation for modern manufacturing, electronic record keeping and regulatory submission.*'

- *'Clarifying the language used to communicate deficiencies observed during cGMP inspections to better describe the purpose and effect of the investigator's observations issued at the conclusion of an FDA inspection.'*
- *'Focusing FDA resources on inspections that are likely to achieve the greatest public health impact (e.g. sterile drug manufacturing).'*

At the same time (February 2003), the FDA withdrew the draft guidelines covering validation, time stamps, maintenance of electronic records, electronic copies of electronic records and glossary of terms and replaced them with a new draft guidance document entitled 'Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application'.<sup>9</sup> This new guideline (which was published in final form in August 2003) clarifies where Part 11 should be used but more importantly, gives an insight into which systems and which aspects of a system the FDA are more likely to be concerned with during an inspection.

The new guideline states that it is the intention of the FDA to 'narrowly interpret the scope of Part 11'. There is also recognition that in some cases hybrid systems should be allowed (where electronic records are printed and the paper version signed). There is even allowance for the fact that systems implemented prior to August 1997 may not be required to comply with Part 11 to the same level as systems implemented after that date. Unfortunately, this could lead to the assessment that we can forget about Part 11 when that is not the case. The FDA have sensibly re-positioned the guidance to reflect what they believe is important. And central to this is the concept of a risk-based approach – and focusing one's energy and resources on areas of highest risk.

The guideline makes it abundantly clear that it is the predicate rules (GMP, GLP and GCP) that we have to comply with. Part 11 helps us to clarify what needs to be done if we wish to use electronic records and/or electronic signatures – just as it always did. The bottom line, which applies to all systems – even those in place prior to August 1997 – is that *'all systems must comply with all applicable predicate rule requirements and should be fit for their intended use'*.

At the time of going to press it is too early to say where this initiative – and in particular the risk-based approach – will lead. There is already support from the Pharmaceutical Inspection Convention (PIC) documented in their 'Good Practices for Computerised Systems in Regulated GXP Environments'.<sup>10</sup> However, if we look at how validation as a topic has grown in significance since it came on to the regulatory scene in the 1980s, then we may have some idea of where this road may take us.

In the remaining part of this chapter, we will consider some of the major aspects of computer systems and/or the application of computing technology. I have split them into 'big picture' issues and issues specific to each system.

At the end of the chapter is a checklist that can be used when performing "gap analysis" in an IT Department or system audit.

## 37.4 'BIG PICTURE' ISSUES

### 37.4.1 Responsibilities

The senior management of a test facility or manufacturing operation has the ultimate responsibility for ensuring that computer systems used within their department or site are 'fit for purpose'. In a regulated environment the responsible person for each and every computer system should be clearly identified. Often this responsibility will be devolved to someone else and the important issue then is to ensure that the person who has this responsibility understands what that means and has the authority to ensure the system does what it is expected to do.

The responsibility might well be split, with some aspects such as the management of the 'operational aspects' (installation of equipment, maintenance, copying data to a removable media, etc.)

being undertaken by one department, while management of the day-to-day operation and support of the system is done by others. In most cases, there will be a number of individuals who contribute together to ensure that the computerised system performs adequately. All of them need to understand what they are responsible for and perform their role competently.

### **37.4.2 Personnel**

All personnel who select, manage, use or support computer systems that may be used in a regulated environment need to have a clear understanding of the regulations and how they apply to the computer systems they use. They need to have adequate training to perform their role and may have gained useful experience during their careers that should make them more effective.

They will work within a framework that provides them with support as well as controls to ensure that everything is working as intended. They will have policies and procedures and in the GXP world they will have a Quality Assurance (QA) function to help them.

Enthusiasm and experience are two great attributes for anyone who is involved with computerised systems. Realism is another useful attribute and is particularly valuable during the early stages of any system. Good people can often mean the difference between a computerised system fulfilling its expectations and just doing a job. Of course, even the best people cannot make a poorly performing system work well. But having effective people in key roles is probably the most important factor to ensure that a computer system is compliant.

### **37.4.3 Policies**

Because policies are the foundation stones for the quality management system (QMS) and set an expectation level that has to be met by everyone in the organisation, they need to be clear and concise. They need to cover the 'big picture' issues and to justify why these issues are important. In order to do this, they should fit readily into the overall aims and objectives of the organisation. Done properly, they will provide the framework for the procedures and also for any decision making that has to be undertaken, for example when conducting a risk assessment.

For computerised systems there are likely to be a number of policies that cover all the key aspects and key phases of a system. But making sure that everyone in the organisation understands why a policy is important is just as important as the details of the policy. It is also unlikely that the justification for any policy will simply be that it is a regulatory requirement. Indeed, if that were the case then one should feel justified in stating that there must be a better solution.

### **37.4.4 Procedures**

Procedures are another crucial part of the framework for any QMS and everyone who has been involved with the GXPs will know they are important. For a computerised system, the procedures need to cover all the routine and non-routine aspects. As with policies, it is useful if each procedure explains what its objective is and why it is important. The procedures covering development of and technical support for computer systems are likely to be of a different format to those used in routine operations but nevertheless should exist. It is perhaps worth pointing out that the updated ISO9001:2000 standard provides significant flexibility on the details required for written procedures, depending on the training and experience of the personnel who are expected to follow them. For example, they allow for very minimal procedures for personnel who know what they are doing – and why they are doing it (Figure 2).

Documentation stating that procedures have been followed and that work has been properly authorised should exist and be available for inspection during an audit. If systems are being developed then it should be recognised that the development process for software is not a linear

- Security
  - Data Collection
  - Storage
  - Back-up
  - Archiving
  - Maintenance
    - Training
    - Change control
    - Validation
    - Restart/recovery
    - Documentation
    - Audit/inspecting

**Figure 2** *Standard operating procedures*

process and that it is possible that one phase of development may start before the preceding phase is complete. In such circumstances it should still be possible to demonstrate proper control by using an ‘Authorisation to Proceed’ or similar mechanism. This process can also be used to provide the necessary authorisation in the event of an unforeseen occurrence during operation of the system, such as a virus that corrupts the system. A rapid but controlled response in such situations can significantly reduce the impact of such an event.

### 37.4.5 Security

Security is an important issue for all GXP computer systems, particularly those which capture, store or report data that is essential for the business.

The physical access to systems has to be controlled and for systems that collect data, no user should be allowed access without first going through a secure logging in process, such as the entry of a user identifier (UID) and a password.

The Part 11 rule from the FDA provides useful guidance in this area but sensibly leaves the details (such as how often to change passwords) to the company operating the system.

Security also includes controls to prevent unauthorised access, safeguards to prevent viruses and measures to ensure data integrity in the event of a system failure. In the wider sense, security also includes measures taken to protect the business against terrorist acts and sabotage.

### 37.4.6 Data

Although most computerised systems are of significant help in ensuring that events are carried out in the correct sequence, for many systems it is the data that the systems collect that is the justification for their use. Each of the GXP regulations has specific requirements for data and in all cases the expectation is that data stored in a computer system is at least as reliable as that stored on paper. But to complicate matters, data stored on a computer system is not usually stored in the same way as on paper. In a computer system, the elements of the data (such as study reference, patient ID, data type and value) will each be stored in a field of a record. Indeed, some of these elements may not be stored in the record at all but be referenced in another record. These ‘attributes’ of the data (often referred to as *metadata*) are as important as the data value itself since without them the value is meaningless.

There are other attributes of the data that would need to be accessed when reporting the data and each of these could also be considered important. For example, the identity of the person entering the data would typically be stored in a file containing one record for each person and this file would be used for a number of purposes. It may, for example, identify what access rights the individual had to the system. For the purposes of reporting the data, we would need to access the name of



the person who entered it and would not be concerned with the other elements of the record. The problem comes when a change to the record is required, say, to allow an individual wider access to the system. The big question here is whether the record is a 'required record' for GXP (and Part 11) purposes since if it was, then it would (probably) require a full audit trail.

The above example is relatively straightforward and we might expect that any function that allows changes such as the one outlined would only be accessible to, say, the system manager. We might also expect that it would have an audit trail. Unfortunately, this only represents the tip of the iceberg. In most files there will be records that, in one way or the other, contain an attribute which can somehow be connected to the data that is required for regulatory purposes. This could imply that every change to every record must be audit trailed and that is where a risk-based approach can be usefully employed to determine how far to go.

### **37.4.7 Archive (Long-Term Storage)**

As with paper data we need to ensure that data is retained securely for as long as the business requires it. As described above, data is stored differently in most computer systems but it is possible to create an output format that is portable between systems and can readily be presented in human readable form. Current examples of such formats are PDF, HTML, XML and ASCII. This is useful since if we are to keep the data for any length of time, we will not want to have to retain access to the software (and possibly the hardware) in order to access the data. There are some restrictions in what we can do with the data and in many cases, we may want to also retain the original data files in their proprietary formats.

Clearly, whichever format is chosen has to be periodically assessed to ensure that it is still current. The same holds for the media in which the data is to be stored. It is also a good practice to periodically perform a quality control check on actual data stored to ensure that there is no loss of detail when the data is printed.

In their latest guideline, the FDA appears to accept the possibility that electronic data could be either printed out on paper or onto microfilm or microfiche for archiving. Clearly, however, the predicate rules would need to be adhered to. For example, it would not be acceptable to simply print out a part of a tox-path database and archive the printout.

### **37.4.8 Electronic Signatures**

The Part 11 rule from the FDA allows signatures to be captured and stored electronically instead of on paper. This capability was requested by the pharmaceutical industry and what the FDA has proposed is a pragmatic approach that is far less onerous than many (such as the EEC directive 1999/93/EC).

However, there is still a debate as to when a signature is required. In some cases it is possible to argue that what the regulations intend is to establish attributability, for example requiring the person entering data to be identified (with the date and time that was done and other attributes recorded as necessary). My latest discussions with the FDA led me to believe that they may be taking a harder line on this interpretation and have identified over 100 cases in the regulations where signatures are required – including the case described previously.

Part 11 is, of course, an FDA rule and is intended to fit with the FDA's versions of the GXP's. It does not always sit well with regulations from other bodies, notable the OECD GLPs, which require, for example, that GLP data be signed.

It is, however, quite conceivable that a company may want to have a signature, because they believe that it will add value. Part 11 caters for that situation.

Some companies have devised their own rules covering electronic signatures, and in these cases their requirements tend to be more stringent than those of Part 11. It is also possible that with the widespread availability of other legislation covering electronic signatures, the FDA might withdraw their own more lenient requirement.



### 37.4.9 Documentation (Site Level)

In discussing big picture issues, we cannot afford to omit documentation. We have already discussed the essential elements of a successful operation. What documentation do we need so that we can readily demonstrate our compliance with regulations? How can we show that all our computerised systems are under control and working effectively?

Taking a ‘top down’ approach, it must be useful to have a simple diagram of the whole of the infrastructure for computer systems used on a particular site or within a specific department. Associated with this would be a list of all the systems together with a high-level overview of the scope of each system and some relevant details. These may include whether the system is being used in a regulated environment plus other criteria useful to the business. Since the detailed documentation will exist at a lower level, this top-level detail is likely to be minimal. Nevertheless, it can be useful to consider how this information can best be presented to be most meaningful to everyone (including inspectors).

Demonstrating that each system is under control and operating effectively will require more evidence. One possibility that might help us is to allow inspectors’ access to the records of QA audits performed during the life of each system. This is the approach taken by ISO9001/TickIT since their view is that if the QMS is operated effectively and they can rely on the evidence, then their job is largely done. They are then able to spend more time during inspections helping companies improve their processes. Applying this same logic to regulatory inspections would need the buy in of the regulators but with the current emphasis on adopting a risk-based approach perhaps the time is ripe to try it.

## 37.5 COMPUTER SYSTEM(S) ISSUES

### 37.5.1 Selection

In order to assess whether a system is ‘fit for purpose’, those responsible for selecting systems need to be able to assess the ‘compliance level’ of the software/system as well as its functional capability. If the software is general purpose or ‘off-the-shelf’ then it may not have some of the functionality one would normally need. For example, a spreadsheet programme may not have an audit trail of changes to data. This does not necessarily mean that the software cannot be used but it is likely that other measures will need to be put in place to cater for this requirement.

Even for purpose-designed ‘application’ software, there can be problems but it should be possible to verify that the developers did at least have the intention of complying with the GXP regulations and will take some level of responsibility for remediation should that be necessary.

Vendor audits are often seen as a useful process to undertake prior to the acquisition of a system, but there may be more cost-effective alternatives such as requesting that the vendor complete a questionnaire that clarifies what efforts they have made to ensure their systems are ‘fit for purpose’.

### 37.5.2 System Development

Ideally, systems that are to be used in a regulatory environment have been specified and designed with those requirements clearly identified. It may not be necessary for everyone involved in the development to know the details of the regulations or to even have read them. But it does place an onus on the person drafting the requirements document to ensure that essential regulatory requirements are catered for.

The actual development of a system will normally follow a methodology – a Systems Development Life Cycle (SDLC). It may also employ a project management methodology and be subject to periodic risk assessment. Most developers of software will also use a formal QMS such as ISO9001.

Much as the GXP's provide a framework for developing and manufacturing new chemical entities, the QMS in turn provides a framework for developing software of a quality that should ensure it is 'fit for purpose'.

### 37.5.3 Installation and Testing

Surely, the heading has installation and testing the wrong way around. Testing would normally be done prior to installation – except for the very special case where the interaction with plant, *etc.* cannot be simulated. For many systems, however, there is an installation stage followed by an 'on site' testing stage – and that is what the heading refers to. I do not intend to cover the detailed testing that is done as part of the development phase of a computer system other than to state that adequate testing does, of course, need to be done.

The installation of a computer system is often considered to be a critical activity. It should be undertaken with some care as it can easily undermine much of the good work that has been done in the earlier stages. For a new system, the initial installation also establishes the baseline for live operation. There will be some level of 'qualification' of the installation to ensure that the system works as intended. There is also likely to be an 'Acceptance Test' or a 'Validation Test', which also creates a hiatus in activity – particularly when faults are found or the performance of the system is poor. System performance is generally the bigger issue – and could mean that the hardware or the communications network or even the software is inadequate. If a user of a system is unhappy with its performance, then they are unlikely to use it effectively. Consequently, no system should be put into production use until its performance is deemed to be satisfactory. This usually means that an effective loading test that stresses the system under realistic worst case conditions needs to be performed at this time.

### 37.5.4 Documentation

In a regulated environment, each computer system needs to be documented in such a way that the purpose and scope of the system is clear. This will often be recorded at a site level (see above).

Additional details should be considered that would help clarify the following:

- How the system fits within the computing strategy for the site.
- Compliance with company policies.
- Its history (in brief). This could indicate the effort taken to devise or select the system and train everyone in its use. It could also include the number of year's experience the organisation may have with the system.
- When it was validated and where the records of the validation are stored.
- How it is maintained (where maintenance records are kept, whether it is subjected to regular performance reviews or audits, where changes are recorded, *etc.*)
- Who is responsible for managing the system, providing support, installing new versions of the software, *etc.*
- What processes/procedures are routinely used to ensure the system is properly managed and used.

At a more detailed level, there will usually be documentation that describes the use of the system although in many cases this has been effectively replaced by online help.

### 37.5.5 Operational Use

Assuming an adequate framework is in place and everyone who has access to the computer system has been properly trained, the day-to-day operation of a system should be relatively

straightforward. However, as anyone who uses a computer system knows, that does not mean that there will not be problems. It is the ability to handle these problems efficiently that will ‘make or break’ the system in the eyes of its users.

If the problem is serious and could result in the loss of data, then the sooner it is recognised and assessed the better. In some cases, it may mean that a particular function has to be temporarily disabled until a solution is found. In other cases, one may have to revert to a backup copy of the data or even a previous version of the software. Recognising that the problem is serious is often quite difficult as in many instances there will be no error message. Having personnel who have a good understanding of how the system works is clearly advantageous in this instance.

The criticality of the system will help to determine what level of support capability to be put in place. It may also be appropriate to put an alternative manual system in place to act as a backup.

It is worth bearing in mind that the most critical period for any system is the first few months. After this time the operation of the system is likely to become more routine. In the GXP world, however, we cannot afford to be complacent and always need to be on our guard. As I once stated in a training course for OECD inspectors, *‘just because a system works today does not mean that it will work properly tomorrow’*.

### 37.5.6 Support and Maintenance

Even the simplest systems need their ‘champions’. These are the individuals who are committed to ensuring that the systems are going to be effective. They are the people that other users will go to for help. They often provide the first line of support, and if something goes wrong, they are the first to be asked to help resolve the situation.

These ‘super-users’ are very important for the success of any computer system, whether or not it is to be used in a regulated environment. In a regulated environment, their role is even more critical. They will often be able to assess whether the problem is serious – or at least know whom to involve for determining that. They will often be the link between the users and the support organisation and sometimes even the developers (where they can provide useful feedback on possible improvements that could be made to make the system more effective).

Most systems will be supported by a formal support framework. For vendor-supplied systems, this support is usually provided by the vendor but often working in association with the company’s IT department (who will be responsible for the computing infrastructure and will need to control access).

The organisation of support has evolved significantly over the past 10 years and for many vendors is now very structured. Usually they will have a first level of support that will often have experience of using systems in the normal user environment. They can help users to achieve what they wish to do using the system and if there is a problem, they can help to define what that problem is. If the problem needs further investigation that is usually undertaken by a second, more technical, level of support that has access to source code and can make changes, *etc.*

A key performance indicator for any system is the efficiency of dealing with support and maintenance issues. Each step of the process, from recognition of an issue through assessment to remediation should be optimised. The process also needs to check that any remediation that causes a change to the system does not cause further undesirable effects (see Section 37.5.10 on Change Control).

### 37.5.7 Backup/Recovery

For most systems that acquire data, a backup of the data will be taken daily or on a more regular basis with a ‘full’ backup every week. The full backup would include all the data (in whatever form) and may include the software and any configuration settings.

Data backups would often be ‘incremental’, that is only data that has been newly entered or changed would be included. All backup data has to be treated as if it were the original data because potentially that is what it is. If for any reason it is necessary to restore the data from backup, we need to be certain that the integrity of that data has not been compromised.

It may also be useful to record that this retrieval process has taken place in a System Log (see Section 37.5.8).

Since the restore process normally happens relatively infrequently, it is advisable to test the procedure at regular intervals both to ensure that it works correctly and to provide familiarisation with it. Inevitably, when the restore procedure is being used ‘for real’ it will be as a result of a problem and everyone will be under pressure.

When new versions of software are installed, the backup/restore operation is the one that should receive special attention since (along with archiving) it is often given low priority by developers of software.

### **37.5.8 System Log**

This is a tip that I was given many years ago by Paul Lepore (the original spokesperson for the FDA on GLP, now retired), and I believe it is as useful today as it was then. He suggested that every system should have a log that recorded anything that took place which could affect the integrity of the system. This could include updates to the system, audits that were carried out, changes to the network or infrastructure or replacement of (say) a disc drive. It could also include the replacement of key personnel. If the log was ‘on-line’ then for some events it could be updated automatically.

Lepore suggested that inspectors (and auditors) might find it useful to have all this information in one log rather than several and it could help to demonstrate that a serious attempt was being made to control the integrity of the system. Complying with this proposal these days may be seen as an impossible task. Nevertheless, the concept has value and should be considered.

### **37.5.9 Performance Assessment (Ongoing Risk Assessment?)**

Most companies will review their computer system at regular intervals. They will assess whether they are meeting the current business needs (which may have changed since the system was installed) and also whether they are being used effectively. They may also assess whether the ‘Risk Assessment’ has changed (assuming that such an assessment was done in the past).

But there is also the need to review performance on a day-to-day basis to ensure that the system is still performing effectively. This activity, perforce, needs to be undertaken by everyone who either uses or provides support for the system. For some systems it may even be possible to implement some form of internal ‘self-test’ of the integrity of the system (much like double-entry book-keeping in accounting).

### **37.5.10 Change Control**

A workable change control process is essential for systems that are vital to any business. Computer software can be changed to introduce new functionality or correct a problem, but that same change, if not rigorously controlled, can affect other functions that previously worked. Likewise, changes to other component parts of the system including hardware, communications and support infrastructure need to be managed to ensure that systems are still fit for purpose.

If there is an effective monitoring capability already in existence, then the risk is lessened – but only to the extent that problems will be identified faster. Assessment of the criticality of a change must then be undertaken with due regard to the implications of that classification. If every change is classified as ‘urgent’, then this may put an unreasonable load on the parties involved in the process.

An efficient change control process also has to balance the needs of the business (to implement the change) with the risks involved. An unnecessary delay in implementing an essential change can seriously affect the performance of the system, particularly from a user viewpoint. Consequently, getting this balance right will require the close cooperation and commitment of all the parties involved.

### **37.5.11 Migration/Retirement**

The cost of migrating or retiring systems can be very high, often higher than the original cost of the system. Unfortunately, these aspects are usually not given much consideration when systems are acquired and even if they are, standards are likely to have changed during the lifetime of a system that will impact on this original assessment.

Migration from one version of a system to another should be more straightforward than the retirement of a system. The developers of the software will know about the structure of the data and, if they have made changes to that structure, they should be in a position to assess the impact of the change and cater for it in the new version. However, developers may not have access to all the 'real' data that has been collected on previous versions of the system or know the full extent to which the previous functionality was used. There may be a number of reasons for this, confidentiality of data being high on the list. Unfortunately, this usually means that problems of migration are not discovered until the new version of the software is installed. This fact should be recognised and catered for in the installation process by including, for example, a test of the data migration step and an assessment that the data is still acceptable.

Most successful 'off the shelf' systems will have many changes to functionality and data over their lifetime. At some point they may even have a change to the underlying database software that could involve a complete unload of data from one database into another. Indeed, this is often required when moving from one version of software to a newer version. This also has implications on data that has been 'backed-up' since it may mean that when it comes to restoring the data it will have to be processed in some way before it can be loaded into a later version of the system.

The retirement of a system is far more complicated than migration because there is unlikely to be a support organisation in place to retrieve the data and, even if that were possible, the hardware and software necessary to process the data may not be available. In many cases, it may be acceptable to simply provide access to the reports that have been produced by a system rather than the original data in its original 'database' format (see Section 37.4.7 on Archiving).

### **37.5.12 Disaster Recovery**

With computer systems performing a fundamental role in the core operations of most companies, the need for an effective disaster recovery process has been recognised for many years. This fits well into a risk-based approach.

If we can assess what the risk is then we can examine the options that would allow us to reduce the risk to an acceptable level.

It may be that the cost of providing a complete disaster recovery solution is too great, and in this case it may be acceptable to implement a backup process such as recording data onto paper. This may mean that greater vigilance is required when these backup systems are being used to ensure that the quality of the data is not compromised.

Whatever disaster recovery process is adopted, it should be tested like every other process to prove that it fulfils the requirements of the organisation.

### **37.5.13 A Final Word**

New technology should allow us to devise and produce new chemical entities faster and with greater assurance of safety. But as with all innovation, there is a risk – we have to recognise that risk and

take the appropriate action. The regulatory agencies, for their part, can recount many cases where computing technology has been used to misrepresent compliance data. They must act to ensure that public safety is not compromised. It is our job to ensure that we understand their position and not only agree with it, but also comply with the rules that we have helped to create.

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**Evidence for Gap Analysis (GXP Computer systems)****A Overview of (IT) Quality Management System**

- A.1 Is there a Policy covering IT Systems?
  - A.1.1 Does it address Regulatory compliance needs?
  - A.1.2 Is it adequate?
  - A.1.3 Is it followed?
  - A.1.4 Is it reviewed periodically?
- A.2 Is there a Quality Management System?
  - A.2.1 Is it documented?
  - A.2.2 Does it adequately cover IT?
  - A.2.3 Is it followed?
  - A.2.4 Is it 'owned' by everyone?
  - A.2.5 Is it monitored effectively (internally)?
  - A.2.6 Is it (IT) monitored effectively externally?
- A.3 Is Data Security given sufficient emphasis?

**B Personnel and Procedures (top level)**

- B.1 Are key (regulatory) responsibilities assigned?
  - B.1.1 Is everyone aware who has these (regulatory) responsibilities?
  - B.1.2 Are there back-up personnel?
- B.2 Are personnel adequately experienced?
- B.3 Are personnel adequately trained?
- B.4 Is the performance of personnel monitored/reviewed?
  - B.4.1 Is there a formal review periodically?
- B.5 Are there procedures for selection of systems?
- B.6 Are there procedures for installation of systems?
- B.7 Are there procedures for validation of systems?
- B.8 Are there procedures for operation and maintenance of systems?
- B.9 Are there procedures covering security of systems?
- B.10 Are there procedures for back-up of systems?
- B.11 Are there procedures for Archiving of electronic data?
- B.12 Are there procedures for Disaster Recovery?

**C Computer Hardware and Communications**

- C.1 Is there an inventory of all hardware?
  - C.1.1 Is it adequate?
  - C.1.2 Is it up to date and revised regularly?
- C.2 Is performance monitored regularly?
- C.3 Are maintenance arrangements adequate?
- C.4 Are changes to hardware controlled?
  - C.4.1 Are the logs adequate?
- C.5 Are responsibilities for hardware and comms. defined?



- C.6 Is hardware back-up adequate?
- C.7 Is the network 'qualified' (IQ, OQ, PQ)?
- C.7.1 Is wiring, etc. adequate?
- C.7.2 Is there a 'network qualification report'?
- C.8 Are there any 'open' systems?
- C.8.1 Are they adequately managed?

#### **D Computer Software (including Validation)**

- D.1 Is there an inventory of all software?
- D.1.1 Is it complete (includes spreadsheets, etc.)?
- D.1.2 Does it include version numbers, etc.?
- D.1.3 Does it state the compliance status of each piece of software? (in-scope, out-of-scope, validated, etc.)
- D.1.4 Is it up to date?
- D.2 Was each software package selected using the selection process?
- D.2.1 If not, is there a justification for the selection?
- D.2.2 Was a 'Supplier Assessment' done?
- D.2.3 Does it include a 'risk assessment'?
- D.3 Are there any in-house development (including spreadsheet models)?
- D.3.1 Is the Development Life Cycle documented?
- D.3.2 Are all records in place?

#### **E For each Application Package**

- E.1 Is there evidence that the system is suitable for it's intended purpose?
- E.1.1 Does the User Requirement Spec. identify Regulatory requirements?
- E.2 Is the validation plan adequate?
- E.2.1 Is the evidence of Validation adequate?
- E.3 Was each system 'accepted' before being put into operational use?
- E.4 Is there an adequate record of all changes to the system?
- E.4.1 Is performance checked following each upgrade?
- E.4.2 Are the logs adequate?
- E.5 Are 'back-door' modifications to data catered for?
- E.6 Are changes to system settings controlled and logged?

#### **F Access Security**

- F.1 Is physical access to servers adequate?
- F.2 Is physical and logical access to PCs adequate?
- F.3 Are passwords changed regularly?
- F.3.1 Is the mechanism for password change adequate?
- F.3.2 Is there evidence of misuse of passwords?
- F.3.3 Is there evidence that passwords are not kept securely by individuals?
- F.4 Is there monitoring of threats to security?
- F.4.1 Is there a log of such threats?
- F.5 Is e-mail security adequate?
- F.5.1 Is virus protection adequate?
- F.6 Is there a process for handling a virus attack?
- F.7 Are back-up processes in place (if systems are unavailable)?
- F.7.1 Are these processes adequate?
- F.7.2 Have these processes been exercised?
- F.8 What happens when someone leaves, changes role, etc.?



**G Data Integrity and Security**

- G.1 Are data veracity and security treated as of paramount importance?
- G.1.1 Are electronic records regarded as the 'main' data record?
- G.2 Is data verified adequately at time of collection?
- G.2.1 Is data verified adequately as a data set?
- G.2.2 Are procedural controls enforced by the system?
- G.2.3 Are algorithms used documented adequately?
- G.2.4 Are QC measures in place (and adequate)?
- G.2.5 Are QA checks in place (and adequate)?
- G.2.6 Are data attributes adequate (and stored with the data)
- G.3 Are electronic records stored securely?
- G.4 Are modifications to electronic records properly controlled?
- G.4.1 Is the log of data entry and changes readily accessible in human readable form?
- G.5 Are changes to data attributes adequately controlled?
- G.5.1 Are there records of all changes?
- G.6 Is there a need to allow for data entered by a non-standard route?
- G.6.1 If so, is it adequately catered for?

**H Back-up and Archiving of Electronic Records**

- H.1 Are back-ups performed at regular intervals?
- H.1.1 Is the back-up adequate?
- H.1.2 Is the back-up kept safely?
- H.2 Is retrieval from back-up exercised regularly?
- H.2.1 Is there a record when data has been retrieved (from back-up)?
- H.3 Is there an electronic archive (in the regulatory sense)?
- H.3.1 Is there a need to be able to recover archived electronic records?
- H.3.2 Is there a need to analyse archived electronic records?
- H.3.3 Are the above needs catered for adequately?
- H.3.4 What format is archived data stored in?
- H.3.5 Are all attributes of data also archived?

**J Operational Use**

- J.1 Does each 'computerised system' have a 'System Manager'?
- J.1.1 Is there a log of the time spent by the System Manager in this role?
- J.2 Is there a log of all operational issues?
- J.3 Is the performance of each system monitored and assessed regularly?
- J.4 Is there a log of user comments re. the system?
- J.4.1 Is there a process for closing out problems (bugs, user issues, etc.)?
- J.5 Is there an effective maintenance process in place (for each system)?
- J.5.1 Is it effective?
- J.5.2 Are logs adequate?
- J.6 Is there an effective Change Control process (for each system)?
- J.6.1 Is each change evaluated and authorised?
- J.6.2 Are 'automatic updates' catered for (e.g. virus control software)?

**K Retirement of Systems**

- K.1 Is there a process for the retirement of systems?
- K.2 Has retirement been considered (in planning)?
- K.3 Can data be transferred readily from each system?

- K.4 Are there systems that have been retired?
- K.4.1 Is the data from these systems stored adequately?

**L Use of Electronic Signatures**

- L.1 Are 'electronic signatures' (Part 11) used?
- L.1.1 Is Company registered with the FDA?
- L.1.2 Is each 'signer' accredited?
- L.1.3 Are all rules for e-sigs met?
- L.1.4 Do print outs contain the full name of the signatory, his role and the date and time of the signature?
- L.2 Do 'packages' accommodate e-sigs?
- L.3 Are e-sigs applied to spreadsheets?

**M Risk Management**

- M.1 Is Risk Management used in the formal sense?
  - M.2 Have Risk Assessments been performed?
  - M.2.1 Are there records of decisions taken and possible impact?
  - M.3 Has 'risk assessment' been carried out at the system functional level?
- 

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# **QA Developing a Regulatory Compliance Training Strategy: An Opportunity for QA to Improve Quality and Provide Greater Value to the Business**

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## **38.1 INTRODUCTION: THE RATIONALE FOR QA'S INVOLVEMENT IN TRAINING**

Pharmaceutical companies are facing increasing and stressful challenges to deliver greater performance with less cost in less time, while complying with an increasing number of regulations and guidelines such as ICH GCP and the Clinical Trial Directive. This puts a tremendous pressure on the skills base – both technical and managerial – on all companies, whether large, medium or small.

To help manage this process, an increasing number of Quality Assurance (QA) units are playing a major role to facilitate the development of a training strategy, particularly regarding the GXP (this covers regulatory good practice such as GCP, GLP and GMP) technical skills for research and development professionals. This fits naturally to the QA unit's role of improving quality and ensuring regulatory compliance. It is also a way for the QA unit to raise its profile and add greater value to the business.

This chapter describes a step-by-step approach to how the QA unit can develop a regulatory compliance training strategy, and thereby enhance its role in GXP training management. Whereas Chapter 39 concentrates on the training and record keeping necessary to comply with GXP requirements.

This chapter explains the techniques that the QA function can use to play a vital role in successfully helping one to develop a training strategy to deliver compliance with the regulatory requirements. The following aspects are covered:

- Towards a training strategy
- Targeting the value of the strategy
- Developing a training strategy
- Diagnosing regulatory compliance training needs
- Options and planning

- Sourcing your training strategy
- Assessing the value of the training
- Summary, conclusion and next steps.

## 38.2 THE ROLE OF QA IN REGULATORY COMPLIANCE TRAINING

Training departments, trainers and managers responsible for developing research staff are now faced with the need to deliver quicker as well as to deliver more effective and lasting training solutions to comply with the regulated environment. The QA units can play a vital role in developing regulatory compliance training strategies based on their knowledge of GXP compliance issues. The training solutions not only need to eradicate existing gaps in the skills, but also to build world-class competencies for pharmaceutical staff. They also need to ensure that regulatory inspectors do not find major gaps in R&D staff's skills.

Regulatory inspectors now place considerable emphasis on checking that all those involved in drug development have received relevant GCP training. This is the case regardless of where the staff work – for the sponsor or at the study site. This therefore encourages sponsors to focus on implementing very thorough training programmes for their R&D staff, and also for study-site staff working on sponsor studies.

For example, GCP inspectors and ISO external auditors expect the training records to be up-to-date, with documentation of who attended the training, who the trainer was and what the agenda and training documentation were that the delegates received (Chapter 39). The QA units are now increasingly helping the training management to ensure that an adequate system for recording and storing this documentation exists and is readily available to inspectors.

It is also not unusual for the QA unit to run both induction and refresher courses – focussing on regulatory requirements (*e.g.* covering ICH GCP in the clinical research and associated function areas). This helps one to ensure that the staff's knowledge of these important GXP areas is of a good standard.

Another area of QA's input is in prioritising training needs. Irrespective of the size of the company, resources may be limited to spend on training research staff, so that all investments in training need to be focussed on providing tangible, value-led training solutions in order to specifically improve R&D performance. The QA department is therefore in an ideal position to play a vital role to ensure that the investment in training is focussed on the most appropriate aspects of GXP compliance.

This calls for the development and skilful execution of a pharmaceutical training strategy specifically geared at meeting regulatory compliance requirements. This does not mean just responding to individual needs as they arise, putting up reactive solutions to training issues or sending individuals on public courses. Rather, it entails building a regulatory compliant training strategy. This strategy needs to be resilient in the face of day-to-day on-the-job pressures of running drug-development programmes and to adopt the GXP standards.

## 38.3 TOWARDS A TRAINING STRATEGY

Developing a training strategy, which achieves value for the business, is a highly specialised skill. Developing a training strategy requires skills that are not a normal part of the QA role. For the training carried out most effectively, the QA unit will benefit both in developing a competence in training-needs analysis and in the process of developing a training strategy.

The above goal may be achieved in a number of ways; for example, the HR may be able to train QA, or the QA staff might attend a "Train the trainer course". Another helpful approach is to use an external facilitator to gain this expertise, with the benefit of (hopefully) achieving world-class regulatory compliance skills and standards.

The development of an appropriate, focussed training strategy is thus an imperative in order to retain and harvest the full value of key training interventions. Also, it needs to be sourced appropriately, and not just by the easiest and most obvious solution on the marketplace.

A “Regulatory Compliance Training Strategy” can now be defined as follows:

A regulatory compliance training strategy is a value-added, implementable plan for addressing gaps in both current and future skills so as to meet regulatory requirements, and with clear prioritisation.

A regulatory compliance training strategy links the organisational and business goals, and the individuals’ needs. The regulatory compliance training strategy must be dynamic enough to take into account changes both in the organisation and outside it (*e.g.* new regulations impacting on drug development such as the GCP clinical trial directive).

The ingredients of this definition can now be dissected as follows:

- Value-added – it should not only address the specific performance improvements, which will be achieved through improving skills, but also provide a business case for its rationale (*e.g.* the training intervention should be aligned to the drug-development plan).
- Prioritised – this should not merely take account of relative attractiveness and difficulties, but also of its urgency.
- Implementable – it should be carefully tested out against the likely barriers so as to deliver its full value.
- Plans – it should give a coherent overview not only of key objectives but also of options and actions (*i.e.* the “how”).

The regulatory compliance training strategy should not just be remedial – it should also address significant improvements in skills and also gaps between current skills and also ones required to meet challenges in the future regulatory environment. To explore this in your organisation try the next exercise:

*Reader Exercise*

How good is your regulatory compliance training strategy?

Now score your “ regulatory compliance training strategy” as follows:

<i>Very strong indeed</i>	<i>Strong</i>	<i>Average</i>	<i>Below average</i>	<i>Weak</i>
<i>5</i>	<i>4</i>	<i>3</i>	<i>2</i>	<i>1</i>

Value-added focus

Prioritisation

Implementable

Coherence and focus of  
plan

Focus on remedial needs  
for GXP compliance

Focus on significant im-  
provement needs to ensure  
regulatory compliance

*Notes:* Score: 25–30 Excellent, congratulations on your score (but are you sure?)

Score: 15–20 Reasonable, but could do better

Score: 10–15 You need a regulatory compliance training strategy

Score: 5–10 Poor, you may find it helpful to take advice on how to develop a regulatory compliance training strategy.

### 38.4 TARGETING THE VALUE OF THE STRATEGY

Before we look at developing a GXP training strategy let us now look at what value it might add.

“Value” comes from the idea of “economic value”. Ultimately, all business activities only have a point if they can generate – directly or indirectly – some cash flow. Even much of the value of staff (from being in the business) comes from having a job with growth potential and security – and this comes ultimately from cash flow.

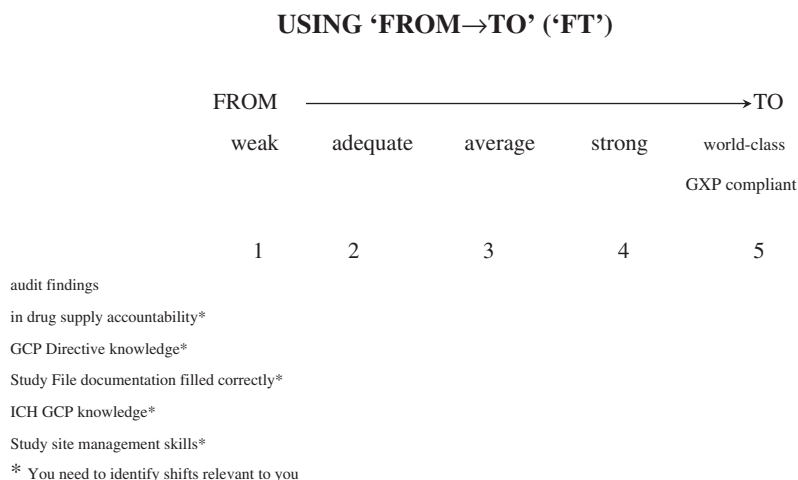
Economic value comes from training in a variety of activities, for instance, in drug development:

- Insightful and visionary decision-making in drug development (*e.g.* development of lifestyle drugs such as Viagra).
- Avoiding errors, disruption and re-work (*e.g.* effective monitoring of clinical trials to reduce the number of data queries and running pre-inspection audits to reduce findings).
- Accelerating processes (*e.g.* faster patient recruitment through CRAs more effectively motivating investigator site teams).
- Improving the adoption of technical know-how (*e.g.* implementation of an electronic data capture system).
- Aligning behaviour (*e.g.* clinical research staff and data management understanding each other’s needs, thus enabling them to produce CRFs which facilitate more accurate data collection as well as are easy for data entry personnel to enter the data from).
- Shifting the mind-set (*e.g.* clinical research staff now welcoming audit and inspection as an opportunity to show how GCP compliant their processes are).

Once value-creating activities have been initially targeted, our next step is to scope these activities in more detail.

Each of these value-creating activities is therefore now targeted in terms of the “From-To’s” of shifts – which will ultimately generate economic value. This can be expressed as a “From-To” or “FT” analysis (see Figure 1 for some examples of the shifts).

This “From – To” analysis can be used to help one assess the gaps in expertise in a particular skills area so as to determine how to close this gap, and to help one assess the effectiveness of the training intervention. It can also be used to monitor the improvement and assess if the targeted improvement has been reached in regulatory compliance.



**Figure 1** An example of “From-To” or “FT analysis”



Some pharmaceutical companies are now starting to assess the value to the business of implementing regulatory compliance training strategies. However, this value-based mind-set is perhaps a new one both to pharmaceutical companies, generally, but even more so for implementing research and development training. Each training initiative should have a business case which specifically targets its value albeit approximately. For example, the QA function might focus specifically on the value of reduction in inspection findings.

The “From-to” analysis is of great help in the first stage of developing a regulatory compliance strategy – its “diagnosis” phase – as we now see in the next section.

### 38.5 DEVELOPING A TRAINING STRATEGY

Figure 2 now is a proven process for helping you to develop an effective training regulatory compliance strategy. In this we distinguish between:

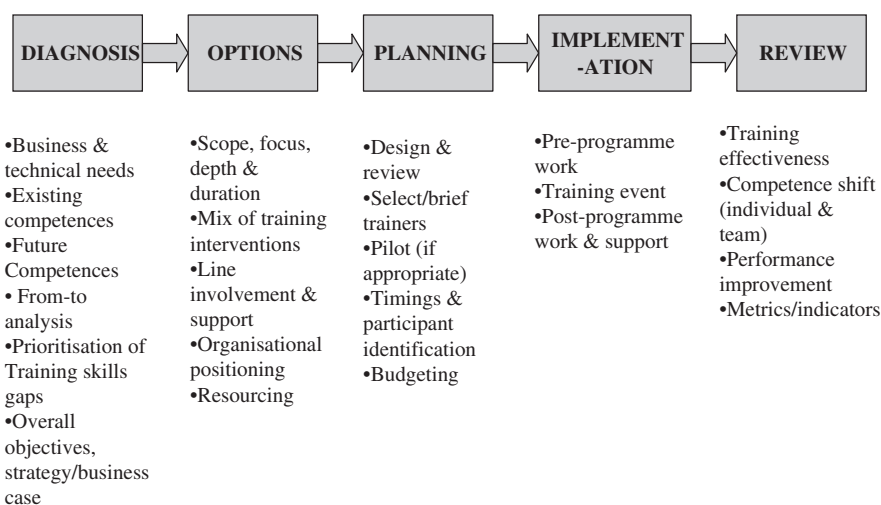
- Diagnosis (of current position)
- Options
- Planning
- Implementation (roll-out)
- Review (of training).

We now focus mainly on the first of these three phases of the process: diagnosis, options and planning.

### 38.6 DIAGNOSING REGULATORY COMPLIANCE TRAINING NEEDS

Diagnosis of current position typically begins with some focussed competency analysis. Competency (*i.e.* skills) analysis involves collecting data and can easily become a major exercise, and one in danger of becoming an end in itself. This is particularly true in the pharmaceutical industry where there are very many technical GXP specialisms.

A good starting point is to review the relevant current research and development procedures to identify the primary research job skills, task skills, and scientific/technical and interpersonal skills.



**Figure 2** Stages of developing and implementing a training strategy

A range of approaches can be used to gather data including structured interviews, questionnaires, focussed discussion groups, audit findings, formal or informal feedback including information collected on training needs from appraisals. All these methods need not be used, and often a sample of structured interviews of both managers and staff regarding a particular job function provides very informative data. This is a particularly flexible approach to obtaining insights, which people are less likely to provide when simply answering a standard questionnaire.

Before collecting data it is essential to win on board, line managers, HR and any training functions in the organisation so that QA function ensures there is no duplication of activities. It is also essential that the initiative is clearly focussed on business needs and gets the buy-in from all the key stakeholders.

When collecting data for carrying out the training-needs analysis, it is worthwhile to avoid limiting the collection of data purely on obvious GXP skills – since some of the interpersonal skill areas will be interdependent with GXP areas, and indeed this can play a vital role in ensuring compliance. For example, it is very important that the sponsor staff, visiting study sites, are able to influence and motivate difficult investigators (a common problem encountered by clinical research monitors), and these are crucial skills to help facilitate compliance.

The data collected during the diagnosis phase will then be reviewed and analysed. This allows you to evaluate the initial gap between the present competence (*i.e.* skills) and the skills required now or in the future. An initial regulatory compliance training gap analysis can then be drawn up by distinguishing between the following:

- Where you are now and where you need to be now.
- Where you are now and where you need to be in the future – to become “World Class” in R&D quality compliance.

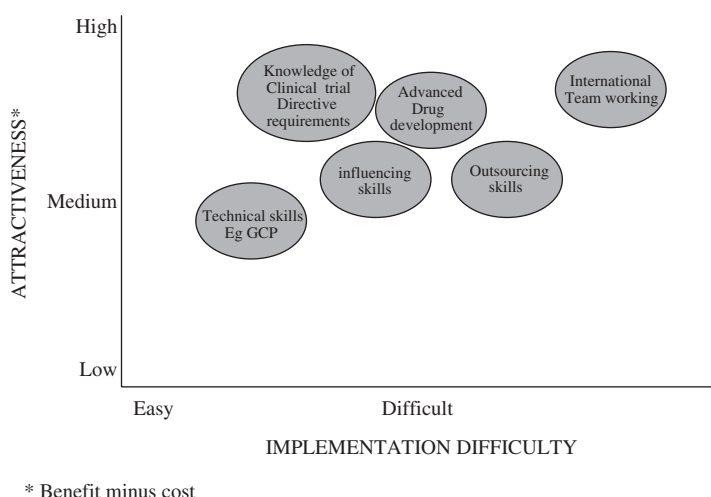
A diagnosis report can then be produced to explain the purpose of the specific training-needs analysis, the methods used to collect the data and the skills/performance gaps and initial solutions for managing these needs. Some of these needs will be specific training solutions and others will be other forms of organisational support (*e.g.* user-friendly SOPs, performance management).

One should ideally be world class in everything regarding regulatory compliance and in addressing all the gaps in skills identified from the training-needs analysis. However, this may not only be unrealistic but may actually have you spread your training resources too thinly. This means that the training strategy needs to be skilfully prioritised, as we will see in the next section.

### 38.7 OPTIONS AND PLANNING

As the training-needs analysis is likely to identify a large number of training needs, it is very helpful to prioritise areas so as to identify areas that should be addressed first in order to optimise effectiveness. It is useful to compare their potential attractiveness and implementation difficulty to carry out an initial prioritisation of training competency gaps. This can be achieved using a technique called the attractiveness–implementation difficulty grid (or “AID” analysis) – Figure 3 shows some examples of possible regulatory compliance training gaps. This output will vary depending on the particular findings of the training-needs analysis and will not be the same for all companies.

It is invaluable, here, to differentiate between continuous improvements (which entail maintenance of current capability or moderate enhancements of it) and a major shift in capability, which will have a major impact on regulatory compliance performance. This will sustain itself readily into the future, which we see in the following two examples.



**Figure 3** Attractiveness-implementation difficulty grid (or "AID" analysis) for prioritising gaps in training skills

### 38.7.1 Example One – Training Monitors

An example of a major pharmaceutical skills shift would be that over the last few years contract research organisations (CROs) have realised that they need to spend as much as 6 months on intensive training to equip new, untrained monitors with the skills to monitor clinical trials before new joiners can monitor sites alone. This has enabled CROs to satisfy the pharmaceutical companies that they will achieve adequate GCP quality standards for monitoring.

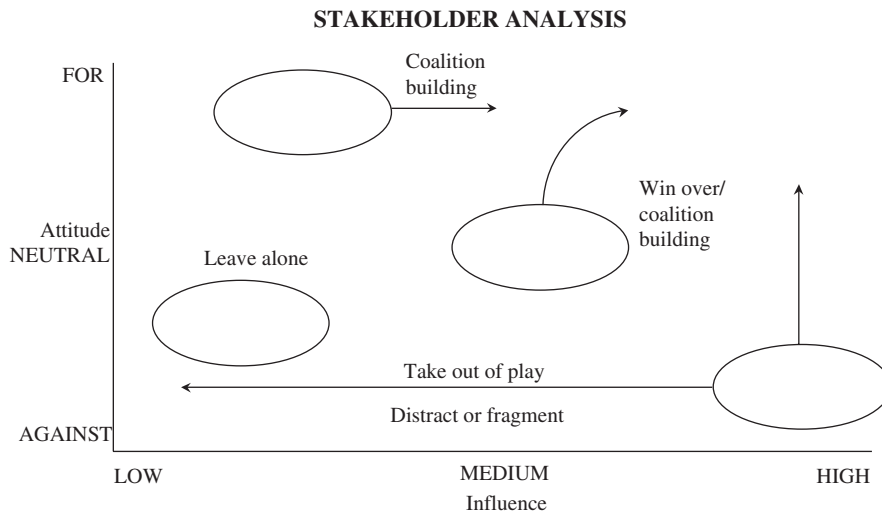
### 38.7.2 Example Two – Electronic Data Capture

Another example is in the area of electronic data capture (EDC) where some companies are looking to run 90% of their clinical trials using EDC to decrease the time taken to enter clinical trial data. This represents a major change in the ways clinical research staff and investigator staff work. For EDC implementation to be effective, major training initiatives are needed so as to facilitate this change in the method of data collection. This is also essential to ensuring compliance with computer validation quality standards (such as the FDA's electronic records and electronic signature regulatory requirements). Inadequate training in this area has been reported in FDA inspections.

Another major change that the industry is starting to look at is a more comprehensive training of study-site staff. On top of this, there are initiatives, the influencing and motivational skills of clinical research staff (to enable them to persuade study staff to take their GCP responsibilities more seriously and undertake the study to a higher GCP quality standard). Additional areas of need include that of training the increasing number of clinical trial administrators, and knowledge management of new regulatory requirements as well as changes in regulatory requirements.

Not many major training initiatives can be attempted simultaneously. Following the Japanese philosophy of breakthrough or "HOSHIN", it is best to implement only between one and three at a time, especially at the beginning of their implementation. By staggering major GXP training initiatives over time (and through the subsequent effective implementation) possibly five or six can be accomplished in an 18-month to 2-year period.

Once a number of strategic GXP training priorities have been identified, it is also essential to look at their key interdependencies. All too often, training initiatives take place as relatively self-sufficient initiatives while their full success – and the value generated – are highly dependent on a number of interdependencies being actively managed.



**Figure 4** Stakeholder analysis

To achieve full alignment of these interdependencies needs considerable positioning and communication of each initiative with the key players involved. It is imperative to use a further visual method of analysing this through stakeholder analysis (see Figure 4). Here we see stakeholders (who will include decision makers, advisers, implementers and recipients) analysed between their respective attitudes (“for”, “neutral” or “against”) and their levels of influence. This technique is very useful at the “Options”, “Planning” and “Implementation phases” of our five-stage process (see Figure 2) again.

From experience, all the analytical techniques covered in this chapter need to come into play to evolve an effective regulatory compliance training strategy, (especially gap analysis, “AID” (prioritisation analysis) and stakeholder analysis). In terms of ownership, the QA function (along with the training and/or HR department) should ideally act as specialist advisers on how training issues can be best addressed, implemented and monitored. But the QA’s role should not be to actually take over (either wholly or primarily) the training interventions except in exceptional circumstances – to avoid spreading itself too thinly.

Besides obtaining the ownership of senior management in the relevant departments (especially using stakeholder analysis – see Figure 4) from the very start it is highly advisable that management are then involved in the detailed planning and even in the implementation of the training programmes and the subsequent learning-support processes.

Table 1 compares and contrasts the respective roles of line management and QA function/training department:

You may now find it useful to work through the following for your organisation:

*Reader Exercise*

- To what extent does the model of the various roles (as defined above) reflect practices within your organisation?
- Where this does not happen, what are the problems and costs that arise as a result of this?
- Does line management currently have the skills and mind-set to accomplish this role? (If not, what training and other support are required?)
- Does the QA unit and training department currently have the skills, mind-set and credibility to achieve this? (If that is not the case, what training resources and repositioning does this imply as needed and should these be sought externally – either in whole or part?)

**Table 1** Roles of line management and QA function/training department

Line Management – roles	QA unit/training department – roles
<ul style="list-style-type: none"> <li>• Own the strategy</li> <li>• Sponsors all training</li> <li>• Makes the business case for the training initiative</li> <li>• Is visibly involved in delivery of the training</li> <li>• Is responsible for assessing the value added, return on investment (ROI) of the training initiative</li> </ul>	<ul style="list-style-type: none"> <li>• Advise on the training strategy</li> <li>• Administer the programmes (wholly or partly depending on the situation)</li> <li>• Provide input to the business case</li> <li>• May co-ordinate (and where necessary implement) delivery of some GXP areas in the case of QA unit</li> <li>• Advise on how to get maximum value following training interventions</li> </ul>

When there is a close and truly symbiotic relationship between QA, senior management and the training department, then the default training strategy, which is likely to occur, can be characterised as:

- A core of standard, regular in-house training programmes which address past training needs—partially and as one-off courses without real follow-up and follow-through;
- The value/ROI (return on investment) of training is frequently assessed primarily by “happy sheets” rather than by genuine, tangible value-added assessment;
- New needs are identified sporadically by senior management, and are frequently not well diagnosed. The training department/training function is then expected to react fast to put something in place, and this sometimes fails to address the real needs effectively;
- Line managers and the training department/training function are reactive to individual requests for training, with the result that too much relevance is placed on relatively more expensive and untailored public programmes. When individuals return to their companies, the learning (especially of less technical skills) dissipates as the organisation-at-large’s mind-set is unchanged.

This now brings us to the issue of sourcing your training strategy, which is a sub-part of the “Planning Phase”.

### 38.8 SOURCING YOUR TRAINING STRATEGY

Training solutions can be found in a variety of forms, and not just through standard courses.

While standard public and in-company courses do have their place, a focus on them as being *the primary* sources of training may be inappropriate and misplaced. Probably the best combination is that of tailored internal courses with follow-on project work and selective mentoring – alongside a lower reliance on standard courses for core, predictable skills training. A tailored, in-company approach is particularly suited to:

- Technical GXP skills; where these are company- or department-specific
- People skills – communication, motivation, influencing, change management, *etc.*
- International matrix team-building.

### 38.9 COMBINING INTERNAL AND EXTERNAL TRAINERS

As mentioned earlier, a very powerful delivery combination is to source tailored programmes with some internal training source and an external provider who can add an outside perspective. This

will help one (a) to stretch training standards (b) to benefit from course design already well practiced elsewhere. The choice of an external provider can be based on the following criteria:

- Technical ability in pharma R&D and GXP, track record and credibility of training research and GCP QA professionals
- Training skills and style
- Their willingness to understand the company and deliver a truly tailored training solution
- Likely fit with the company's culture (and the relevant department)
- Their flexibility and responsiveness generally
- Their focus on the really value-added (rather than on just doing the training and satisfying the "happy sheets")
- Costs.

### 38.10 ASSESSING THE VALUE OF THE TRAINING

It is essential to evaluate the value of training initiatives and to assess the value of the training interventions. The reasons for evaluating the training are

- checking that the programme objectives have been met
- to see whether the learning transfer has actually taken place
- measuring changes in performance on the job
- checking that the training interventions have contributed to a more effective organisation
- to modify future programmes.

More specifically, considering how improvements in quality could be measured by looking at reducing errors in data, reducing the amount of missing data, and reducing illegible and erroneous data. Also, improvements in costs could include reducing queries, reducing monitoring workload and reducing data-management workload.

Reducing time could include the following: shortening the set-up times, shortening time of "last patient last visit" to "frozen database", from "approved protocol" to "written report", and from "start of development program" to "expert report".

The QA can take a lead in assessing the value to come out of the training initiative. Sometimes these assessments are termed "metrics" and/or key performance indicators. To make these assessments, measures should be taken before starting the training initiative in order to provide a baseline for the predicted and hoped-for future improvement in performance.

Quality Assurance units are increasingly setting up or are involved in setting up databases to collect such information. With very little additional work by QA, this data can be used to assess the value of training initiatives. The QA can thus play a significant role in improving GXP quality and other quality standards for the company.

### 38.11 SUMMARY, CONCLUSION AND YOUR NEXT STEPS

Pharmaceutical companies are putting ever-increasing demands on their staff to perform to the level of world-class quality standards of R&D, and this cries out for the development and implementation of an effective regulatory compliance training strategy as has been outlined (and with QA playing an important role in such an initiative). To develop a truly robust strategy for GXP compliance requires the symbiotic work of senior managers who genuinely see value added from training; a business-focussed, strategic QA unit and also the training department.

The training strategy should have at its heart a number of key (prioritised) major GXP training initiatives (and also of continuous improvements). These should be diagnosed with line managers, be well positioned and should then be sourced in an innovative way that matches the need.

Training solutions should be tailored as closely as possible, preferably with far less reliance on public courses and perhaps more on internal, tailored courses. Evaluation of the value of the training intervention is a key part of realising the value of the training intervention. The QA functions are often ideally positioned to assess this.

Given the increasing regulatory and other changes that are taking place in the pharmaceutical industry, it is therefore imperative to be flexible and responsive to changes to help ensure future compliance in this highly regulated environment. The QA functions are well positioned to help the company meet these needs. So are you ready for the challenge? Perhaps the first step would be to work out the scope of your regulatory compliance training strategy, along the lines of Figure 2.





# Training and Staff Records for GXP

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## 39.1 INTRODUCTION

The good research practices, whether manufacturing, laboratory, clinical or ISO quality management system, have a common element relating to personnel at their core. This is that all personnel involved should have sufficient training and experience to perform their duties. This can be considered as a twofold requirement. In the first instance, the individual must be fully capable of performing any task required of them in a competent and satisfactory manner. However, of equal importance is the need for all personnel to be aware of the requirements placed upon them by the specific good practice under which they are operating. At the simplest level this can be achieved, for all new recruits, by incorporation of an element covering these requirements into any 'new starter' programme that is run at the facility. At best, this can only provide a basic overview and should always be followed up by further training. Ongoing training is also required not only to make personnel aware of any changes in rules and regulations but also to act as a refresher course for existing requirements. This chapter should be read in conjunction with Chapter 38, which advocates a greater strategic role for QA in GXP training management.

In general, personnel can conveniently be divided into two groups: those working in the quality assurance unit (QAU) and those who are not. The training requirements of these two groups will be different, as will be the requirements for new and existing staff in these categories. However, a further complication arises especially in the areas of field studies conducted under GLP (Chapter 24) and studies conducted under GCP (Chapters 1 and 8), whether clinical or veterinary. Many individuals in these studies will be independent of the sponsor company but are still bound by the requirements of the specific good practice. Training of these individuals is just as important as the training of the company personnel and in some cases could be considered as more important since it will be these external workers who will be largely responsible for the conduct of the study. It is the aim of this chapter to address the different training requirements, and to suggest methods that can most effectively be used in developing and delivering training programmes. In the following sections the generic term GXP has been used to indicate where any of the specific good practices may be applicable.

## 39.2 TRAINING OF QUALITY ASSURANCE UNIT PERSONNEL

Quality Assurance (QA) personnel can be regarded as the hub of the good practice wheel within any organisation. The purpose of the QAU, as highlighted in the Preface, is to assure management that any regulated studies or procedures carried out are fully compliant with all aspects of the GXP.

Clearly, therefore, it is not sufficient for a member of the QAU to be simply aware of GXP. The major job element of the QAU employee revolves around the GXPs, and it is essential that each person in the unit has a full working knowledge of these and keeps up-to-date with any changes that may occur. An additional role of the QAU employee may be to provide training in GXP to other personnel in the organisation. As such, the trainer must have a comprehensive knowledge of the subject.

Members of QAUs tend to come from disparate backgrounds, although in general, the majority will have a scientific background. In the case of GCP units, it is often found that personnel may have previous experience in nursing. The reasoning for this was the understanding of management that a good working knowledge of the scientific or medical procedures involved in the studies would be necessary to assure compliance of the studies with GXP. Although the role of the QAU is largely administrative and deals with the processes involved in the studies rather than the actual science or medicine, it is still the case that the majority of the staff of a QAU will have a scientific background.

Undoubtedly such a background can prove advantageous. When inspecting a laboratory study, the auditor with an understanding of the science behind the procedure being carried out can assess whether it is being followed correctly with a greater chance of success and thereby attract greater credibility and respect as auditors. Equally, clinical auditors with a medical background may better understand the correct reporting of treatments if they are familiar with the specific disease process. On the negative side, however, there is the danger that the scientifically based auditor may observe aspects of the science with which he or she disagrees. In such situations, the temptation may be to criticise the science, which is not the role of the auditor. During any training programme therefore, as well as teaching what should be done, it is equally important to emphasise what should not be done.

The responsibility for having adequately trained staff rests with management. In this respect training in GXP ultimately becomes the responsibility of the QAU manager, for not only QAU personnel but also general facility personnel. Staff training needs can differ considerably, depending on not only the size of the unit but also the experience of the personnel employed, and it is up to the manager to decide what is most appropriate for his or her organisation. In large companies or contract organisations, where many studies are carried out, it may be expected that a large QAU will be required to support these studies. At the other extreme are the small companies that perform few studies and where the QAU may consist of only one person. It may also be the case that this person may have other responsibilities besides maintaining a QA function, *e.g.* as archivist. In this latter case, any training programme will clearly have to be self-driven, and a much greater dependence placed upon external agencies. In the larger QAUs, the development of in-house programmes is more desirable. These can be varied not only to meet the requirements of new members of the unit, but also to maintain an awareness of GXP in existing personnel.

Training external workers poses a different problem. It is still the responsibility of the sponsor companies to assure that these people are adequately trained, often at the start of studies. However, the tendency is for these to be training in the details of the specific study to be carried out and not in the more generic requirements of GXP. Training in this tends to be left to the individuals involved or in many cases overlooked completely. This is clearly not an acceptable situation and efforts should be directed towards ensuring all personnel are fully conversant with the requirements of the specific good practice under which they are working.

### 39.3 ELEMENTS FOR IN-HOUSE TRAINING PROGRAMMES

It is to be expected that a person appointed to a QAU will have certain qualifications to support such employment. These qualifications, depending upon the background of the person, may include previous experience in GXP. It is possible that the person may have been transferred from another QAU, although this may not necessarily be for the same GXP as there is interchangeability,

especially with personnel moving from a GLP unit to a GCP unit. In these cases, very little initial training relating directly to the awareness of GXP should be necessary. There may be the requirement to emphasise particular elements but the basic background understanding should be present. Training can be directed more to the familiarisation of the working practices of the unit and the organisational arrangements within the facility. Similarly for those new QAU members who have previously been working in a GXP environment initial detailed training may not be necessary, as it would be expected that they would bring their previous knowledge with them. However in such situations, it is important to assess the level of this knowledge since the functioning within a QAU requires a much more comprehensive knowledge of the requirements of GXP and the associated rules and regulations than may have been the case in their previous position. For the new employee coming in only with a scientific or medical background, much more comprehensive training will be required. As pointed out above, such a background may be beneficial but will not necessarily involve any previous experience in GXP. Monitoring compliance with GXP is the principal function of the QAU and detailed knowledge of the requirements is a necessity for all personnel within the unit. Comprehensive training to ensure all new personnel have this knowledge is therefore a necessity and not an option. With the different regulations in place and the constant introduction of new regulations and changes to those already existing, it is especially important that all employees keep abreast of these.

It should be remembered that training is simply the education of the individual to allow the performance of specific tasks or to understand different principles. In the case of the QAU member, the endpoint of the training is a sound working knowledge of the regulations and guidelines pertaining to the particular GXP being followed at the particular facility. The purpose of the training should be to enable the person to carry out his or her job in a proficient manner according to these requirements. Upon completion of the training, the person should be able to recognise areas of deviation from the principles involved and be able to advise others as to how compliance may be achieved and, where appropriate, provide recommendations for corrective action. Each member of the QAU should follow a training programme developed to raise his or her performance to the required standards.

Training is a process of obtaining new knowledge, whether information or procedures, through practice and instruction. Too often, training methods involve attendance at formal lectures when other alternatives exist and may be more beneficial in attaining the required aims. It is often more productive for individuals to sit down by themselves and study different documents relating to the topic in hand. Indeed for a QAU, this is usually the only way to operate, since it is unlikely that more than one new recruit requiring training at any given time will join the unit. It would not be a good use of time to commit another member of the unit to provide formal training.

It is the responsibility of the QA manager to be aware of the expertise of the employee and to be able to direct a programme to suit the needs of the specific individual. Initially, a short session with the manager and the employee should take place, during which a brief overview of the specific GXP should be given along with a timetable for a training programme for the employee agreed, including specified targets. Regular review sessions should also be agreed upon, at which the employee can raise any questions and the manager can assess the progress being made and adapt the programme if necessary. It would be expected that within the QAU there would be certain items that could be used as valuable training aids.

### **39.3.1 Regulations/Guidelines**

The most important sources for information regarding the GXPs are the regulations and guidelines that have been issued by the various agencies involved. Within each discipline, different agencies may issue their own particular documents and although the general concepts are essentially the same, there may be slight differences in the individual elements and the interpretation may also

differ. This may be particularly the case when considering the different national legislations involved. However in recent times, the situation has greatly improved with the general adoption of the OECD Principles for GLP. In the clinical arena up to quite recently, the situation was somewhat complicated by the fact that there was no definitive document defining GCP but were more of a plethora of documents, some of which were regulations and others guidelines. Each country had its own requirements and the legal status of these differed from country to country. In the United States, the documents making up GCP were to be found in different sections of the Federal Register. Another consideration was the Declaration of Helsinki, which defines a code of practice to be followed when undertaking research on human subjects. The situation has now greatly improved with the issue of the International Conference on Harmonisation Guideline for GCP, and in Europe the legal status has been clarified by the European Directive 2001/20/EC on Clinical Trials. The GMP European Directive 2003/94/EC and the amendment to Annex 13 covering the manufacture of investigational medicinal products, also tend to clarify and standardise requirements. There are also various other European Commission Directives relating to different parts of GXP that aim to ensure that standards and procedures across the European community are equivalent in national legislation. In any training programme a detailed study of all the regulations and guidelines relating directly to the activities of the particular QAU should be undertaken. The trainee should, however, be aware of the content of other associated documents to provide a broader base for his/her knowledge of GXP.

### **39.3.2 Standard Operating Procedures**

Within each of the good practices, it is a basic requirement that there are standard operating procedures (SOPs) in place, and the QAU is no exception to this. These SOPs should describe the working practices and procedures of the unit and, as such, can be an important training aid for new personnel. By studying these documents in conjunction with the regulations/guidelines, it should be possible to develop a better understanding of the latter. Furthermore, those SOPs describing the operation of the QAU should provide the trainee with guidance regarding the interpretation of the requirements at his/her facility. It is not only important to be aware of and understand the QAU SOPs, but also to have a similar knowledge of the other SOPs covering the activities of the facility. In carrying out audits and inspections it will be these QA staff who will be using as a benchmark for compliance, and it follows that to be able to do this requires a good knowledge of their contents.

### **39.3.3 Other Training Aids**

Members of the QAU within any facility should be regarded as the experts, in that facility, in matters relating to their specific GXP. In this respect, it should be their responsibility to provide training in matters relating to GXP for other personnel at the facility. It may be expected that certain, more formalised aids for use during such training would be present in the QAU. Such items may include a slide presentation, a video or simply outline lecture notes. It is also possible that there may be some form of quiz available for presentation to staff. Whatever the format, such aids also represent a valuable source of information to be placed at the disposal of the new QAU recruits to assist in their own training.

Perhaps the most valuable training aid in the QAU is experience – the experience already achieved by other members of the unit, and also the experience that can be developed by the trainee carrying out his/her job by performing inspections and audits. It is unrealistic for any new member to be expected to carry out inspections and audits in isolation. For this reason many units have introduced a system of mentoring, whereby the new recruit is allocated an experienced member of the unit to provide on-the-job training. Alternatively, the trainee can work with different members of the unit as opportunities for obtaining experience in different types of inspections and audits. In any situation, the most productive system is where the trainee at first adopts a passive role,

simply observing the more senior person at work. Once a level of confidence has been achieved, the roles can be reversed at subsequent inspections. The trainee would now be carrying out the actual inspection with the established QAU member acting as an adviser. As with any training, it is important that all this is documented and when the trainee is adjudged to be able to work alone, a certificate of competence is issued and signed.

### **39.3.4 Advanced Training for Experienced Quality Assurance Staff**

Training is not a one-off event but an ongoing process and once the QAU recruit has reached the end of the initial programme, this should not be considered the end of the learning process. It is essential that QA personnel maintain their awareness of GXP and keep abreast of any changes in the regulatory environment. To ensure this is the case ongoing training should continue for all members of the QAU. This can be on both a group and an individual basis, but it should again be stressed that this does not necessarily have to be formalised to any extent. As outlined in the previous section, experience obtained in actually carrying out the job can be a valuable teacher. As each member of the group carries out his/her work, different challenges will arise that will require decisions and interpretations that may not have been confronted before. These can then provide topics for seeking advice or discussion within the QAU. Clearly, in this respect, the larger units do possess an advantage since interactions between the staff allow advice to be sought and discussions to develop, to enable a consensus to be achieved.

The larger groups also have a further advantage in that different members of staff can be allocated specific responsibility for different aspects of the work for the unit. To ensure that each member of the group maintains a broad knowledge, and to maintain an interest in the work, these roles should be rotated throughout the staff. This in turn can lead to a more efficient and knowledgeable group. A symbiotic relationship can be built up with each person not only learning from the experience of others, but also making his/her own contribution to the pool of knowledge.

The departmental SOPs can also provide a further opportunity for training, especially in the larger QAUs. The SOPs should be reviewed on a regular basis, normally annually, and, if the review is carried out on a group basis this can provide an ideal forum for discussing the working practices of the unit. Since the bases of the working practices are the requirements of GXP, the end result could be considered as a refresher course in GXP awareness. A review of all the QAU departmental SOPs at one time with the whole group should also lead to a standardisation of working practices, ensuring that all personnel are working to the same rules. This is essential to ensure that mixed messages are not given to other groups during audits and inspections.

Members of the QAU may also attend external training programmes. These may be in the form of general conferences or specific topic-related seminars. Costs for these events normally prohibit more than one or two people from any company from attending them. However, it should be borne in mind by those fortunate to be selected that they are attending not as individuals but as representatives of their group. Therefore, on return to the unit, provision should be made for disseminating the information obtained throughout the whole group. This can be done, in the first instance, by preparation of a written report. However, by far the most useful and beneficial process is for the attendee(s) to present a report in a departmental meeting. This will again provide a forum for discussion of topics raised and enable the whole group to benefit. Such departmental meetings can also be used to discuss general topics and problems that may have been identified in audits and inspections, as well as any changes in regulations that may have occurred.

For the smaller QAUs, where there are only one or two people, such training methods and programmes are not feasible. In such situations, the individual must be responsible for his/her own training, and it is unlikely that much help and guidance will be available from other, non-QAU personnel at the facility. Other methods of obtaining necessary information must be used and all of these will depend upon outside sources. One obvious route is attendance at external training



courses, which will be discussed in the following section (Section 39.3.5). On a day-to-day basis, however, other options must be examined. Publications from various organisations can provide useful information, but as technology has advanced the Internet provides possibly the most efficient method of maintaining awareness.

Several journals often include papers covering different aspects of GXP, although these tend to be more generic covering all aspects of research. Examples would be the *Drug Information Journal* and the *Good Clinical Practice Journal*. In the clinical area, the *CQA Adviser* is a newsletter providing a review of recently published information. For GLP and GMP, however, there tend to be fewer specific papers. The most valuable information in all areas is produced by the regulatory agencies. Probably the most relevant of these are now the European Community, the US Food and Drug Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA) within the United Kingdom. The different trade organisations such as the Association of British Pharmaceutical Industries (ABPI), the Chemical Industries Association (CIA) and the British Agrochemicals Association Limited (BAA) also keep their members aware of developments in the regulatory field. However as stated above, the quickest and most efficient way to maintain awareness is through the Internet. All of the organisations discussed have their own websites where the specific documents describing the regulations can be found. The FDA site ([www.fda.gov](http://www.fda.gov)) in particular, besides providing access to all the relevant regulations includes many other items of useful information. For those personnel in QA the process of accessing information has also been simplified by the British Association of Research Quality Assurance (BARQA) through their own web site ([www.barqa.com](http://www.barqa.com)). This is subdivided into the areas of interest, whether GLP, GCP or GMP, each of which provides links and downloads of the most important documents.

### 39.3.5 External Training Programmes

As mentioned, attendance at external training programmes is another method of training and is particularly useful in those smaller QAUs where in-house training is not an option as the trainer and trainee may be the same person. In larger units, it may also be desirable to accelerate the training of an individual to allow him/her to take up the position of a functional member of the QAU as quickly as possible. The gentle progress of an in-house programme would not satisfy this need. The alternative that must be considered is the use of an outside agency. The choice of these and the topics covered is sufficient to meet the requirements of any unit. Courses are available covering general GXP topics, more specific topics relating to items of GXP as well as QA auditing courses.

External courses, on the whole, run over a period of several days and enable the participants to increase their store of knowledge quickly. It is also the case, especially in those external meetings designed specifically for training rather than for examining a specific topic, that workshops are provided to allow the participants to solve problems that they may experience in the conduct of their work. However, care should be exercised in the interpretation of what has been learned since the information provided may not always relate directly to what the individual will be doing at his/her own facility. Some courses tend to be more information oriented than concerned with practicalities. In these cases, the direction can be more towards what the regulations actually state and not to interpretations. This however can be extremely beneficial for the person new to GXP and certainly, attendance at such courses is to be recommended as a method for obtaining the maximum exposure to GXP in the shortest possible time. It could also be argued that interpretations of regulations can also be problematic since often these will be the interpretation as applied by the particular trainer and may not represent the general consensus within the industry or indeed that of the regulators. An unseen benefit for attendees at external courses is the ability to network with other members of the profession. This enables attendees to discuss how any problem is dealt with in other companies and can only serve to increase their knowledge base. For the person



from the smaller QAU unit, it also enables links to be made with people, possibly in the same position as themselves, who can be contacted in the future to discuss common problems.

The number of organisations providing such training courses is too large to mention any specific provider, but all tend to advertise regularly in journals and through mail shots. Identifying a specific organisation to meet specific training needs should therefore not be difficult. Introductory courses are available for each of the GXPs where international speakers cover the regulations and basic practicalities in the auditing of studies. Follow-up courses covering different aspects of the GXPs are then available where topics such as SOPs or computer validation may be presented. In the case of GCP, many of the follow-up courses available are not specifically related to GCP but tend to be aimed at the whole medical research community. A lot of the emphasis in these cases tends to be placed on running a clinical trial correctly, with little, if any, reference to QA. Nevertheless, a member of a QAU would find the courses useful in providing an outline of the process of clinical research as a whole. A final consideration for attendance at an external course is always the cost. Registration fees tend to be relatively high, but this must be balanced against the benefits to be obtained from the rapid training of the individuals involved.

The professional associations also offer courses aimed at their members. The most important in this respect are those offered by BARQA and the Drug Information Association (DIA). Both of these organisations offer basic courses in the GXPs, although in the case of the DIA this tends to be restricted to GCP. The follow-up courses from the DIA are also more clinically oriented. The BARQA offers a series of courses that, as would be expected from an association for QA professionals, deals more specifically with matters relating to QA. There are courses dealing with the basic concepts of auditing as well as more advanced courses to assist the QAU member to develop particular skills. These cover such topics as observation and recording, analysis and report writing and negotiating skills.

Attendance at conferences can also be regarded as another method for increasing the knowledge base of the individual. Conferences also provide QAU personnel, especially those from the smaller units, to network with other like-minded colleagues and discuss and exchange views on different issues. As is the case with training courses, there are numerous conferences run each year, which include topics that are of interest and relevance to the QAU members. It is also the case that the professional organisations have again recognised the opportunity to use their annual conferences to provide additional training opportunities for their members. The DIA, BARQA and, in the United States, the Society for Quality Assurance (SQA), have all introduced sessions before the main meeting that are devoted to training. At the DIA these cover a variety of different topics, again mainly in the clinical and regulatory affairs areas. BARQA and SQA tend to introduce sessions that concentrate much more on the GXPs or personal development skills.

As the role of the QA professional has developed, there has also been the recognition that some form of accreditation or professional qualification was required. For a long time the only such qualification that could be obtained was in the United States at Temple University in Philadelphia. A course entitled 'Quality Assurance in Research' run within the School of Pharmacy led to a masters degree. This course is still available and essentially deals with all aspects of the US Food, Drug and Cosmetics Act requirements for drug research. This includes both GLP and GCP. The conceptual aspects of quality are covered besides the practical requirements of an auditor. In terms of GCP, a historical perspective is presented along with examples of research fraud and a detailed analysis of the IND and NDA regulations. The role of QA personnel is also covered, as is the process involved in FDA inspections. As this is an American course, as would be expected, the main emphasis of the course is on the FDA and its working practices.

After a survey of its membership, BARQA also introduced a qualification for QA personnel in 1991 in association with Anglia Polytechnic University. This course was a one-year, work-based programme of self-managed study at distance leading to a nationally recognised graduate qualification, the Diploma of Credit in Research Quality Assurance. Included in the course were two

3-day residential teaching sessions followed by written assignments and a research project. The intention of the course was to provide the student with a broad knowledge in all the GXPs and not just in his/her own particular area. This course has now been withdrawn as a stand-alone entity, but has been incorporated as the foundation level of a Master's programme, again with collaboration between BARQA and Anglia Polytechnic University. This is targeted at a wider audience, including all those with responsibility for managing the quality processes that contribute to successful R&D. The format is again a work-based programme of self-managed study at distance, but with a timeframe of three years. It comprises compulsory core modules and options to suit particular interests and modules reflecting students' prior experience and qualifications. The syllabus encompasses research techniques, quality management, international operations and general management. The next logical stage is for a PhD and options for achieving this are under consideration.

### 39.4 TRAINING OF NON-QAU PERSONNEL

It must be remembered that it is not only the QAU staff who are involved in GXP. All those people working in areas that are subjected to QA inspections or audits, whether in laboratories, in clinical study centres or in manufacturing facilities, should be fully aware of the requirements imposed upon them. Thus, production staff and support workers (*e.g.* analysts, cleaners, maintenance engineers) need training in GMP, as appropriate to their responsibilities. For some members of the staff, the specific problems encountered at the interface between different GXPs will need to be addressed (*e.g.* see Chapter 9). As previously mentioned some of these, such as clinical investigators and their staff and some field study personnel, will not be employees of the sponsor company. These must be considered separately. However, for the personnel directly employed within the sponsor company, training methods are more obvious. For new personnel at any facility there is normally some form of orientation programme run, which will cover such topics as health and safety and other general items. Such a programme is an ideal place to incorporate a session on GXP. New starters on such programmes can have a varying background, from the recent school-leaver to the experienced scientist moving from academia or another industrial organisation. Consequently, these peoples' knowledge of GXP must also be expected to vary considerably. Any training will, therefore, tend to be general, and in this instance should be aimed more at interpretation of the regulations/guidelines than at a specific analysis of the content. The average worker, whether in GLP, GCP or GMP, is less interested in knowing the full details of the regulations but more concerned as to how the work should be carried out to ensure compliance with them. A background knowledge of GXP will, however, be beneficial in understanding exactly why such compliance is necessary. In all cases, it should be stressed that the regulations are simply a reflection of what practices should be in operation in any good research facility to ensure consistency, accuracy and validity of data.

The question of who should be providing the training then arises. There is a strong argument for this to be a QAU function. It is the members of this unit who should be the most conversant with all aspects of the specific GXP in question, and may be considered to be the experts in their facility. As such, they should be ideally placed to take the responsibility of teaching other personnel. The training methods to be used and the content of the programme are at the discretion of the QAU manager. It is however advantageous to have a standard presentation prepared, which can be delivered, as required, by any member of the QAU. The development of a Powerpoint presentation is an option to consider. This has the advantage that it can be readily revised with a minimum of effort, should the necessity arise. Another option is the use of video or films since these can deliver information much more rapidly and efficiently than the spoken word. Videos are commercially available to cover each of the GXPs that, although some of these are now quite old, nevertheless are still relevant and often give a historical perspective. BARQA has also been associated with production of videos to be used in training for the GXPs. When using such tools in training,

however, it is important to remember that videos do not provide a stand-alone training programme. They are intended as aids for training and should be used by trainers to identify items for further discussion and examination in more depth. They are intended to stimulate the interest of the trainees and thereby enhance the learning process.

### 39.4.1 The Study Director

One group of non-QAU employees working in the GLP area that should perhaps be considered separately are the study directors. This group will require a greater knowledge of the GLP regulations than other members of staff since, as defined in the regulations, the study director is probably the most important person in any study. It is the ultimate responsibility of the study director to ensure that all aspects of the study are carried out correctly. He or she is the individual who ensures that the science of the study is sound, but in doing so must also confirm that the study has been conducted with the GLP requirements of the regulatory body to which the data are to be submitted. Most importantly, upon completion of the study, the study director is required to sign a statement attesting to the fact that the study was conducted in accordance with the principles of GLP. Clearly, therefore, a full working knowledge of these principles is a prime requirement before any person can take on the role of study director. It is inadequate for such a person to be trained only to the level as would be required for the average laboratory worker. The level of training required, if not quite on par with that for the QAU member, should be approaching it.

A person appointed as a study director or investigator should certainly not be GLP- or GCP-naïve, respectively. There should be a background of having previously worked under GLP conditions and having passed through the routine training sessions organised at the facility. The responsibility for future training lies jointly with the study director and the site management. It is important that the study director identifies his/her own training needs and develops these by whatever means are available. A logical source is the QAU, and advice and guidance can be obtained from there. In appointing a study director, the site management are placing a great deal of responsibility on that individual and it is essential that adequate management support be given to ensure that appropriate training is received. In this respect, attendance at external courses should be considered and some of those discussed in the earlier section for QA personnel should also be suitable for the trainee study director. The importance of the study director has been recognised by BARQA and one of the courses that the organisation offers has been specifically designed to cater to this group of people.

### 39.4.2 Non-Sponsor Personnel

Although there are no direct equivalents to the study director in clinical research, the clinical investigator plays a major role and it is essential for this individual to be fully conversant with the requirements of GCP. The same applies to the investigator in veterinary studies and also the local investigators involved in field studies. Besides these individuals, the ancillary staff at all these locations must also be considered. The GXP requirements are that all personnel must be adequately trained to perform their roles. When working in regulated studies there is clearly a requirement that these people should be trained in GXP. It is the responsibility of the sponsor to confirm that the personnel are trained and this is normally achieved by review of curricula vitae (CV) and training records, but the responsibility for the training must remain with the local employers. The difficulty is that in many cases, although trained in the conduct of their normal work, there is little if any reference to GXP. The sponsors do have an opportunity to deal with this at the start of the study. The normal practice is to hold study initiation meetings, which may be on an individual site basis or on a group basis involving all the satellite sites that will be involved in the study. Whichever type of meeting occurs, this offers an ideal opportunity to provide the site personnel with basic training in the requirements of GXP.

### 39.5 DOCUMENTATION OF TRAINING

When a QAU member carries out an inspection or audit, one of the checks for compliance will be whether personnel have been adequately trained. This will be done by an examination of the appropriate documentation. It follows, therefore, that there should be clear evidence of all training that has been received by an individual. This would apply equally to members of the QAU, as well as other personnel in the facility. The standard practice is for a training record to be included as part of a person's CV as a separate appendix. The method of documentation will vary depending on the type of training that was undertaken. For external courses, especially those devoted to training, it will often be the case that a certificate of attendance will be issued at the end of the session. This certificate, or a copy, should be in the training record. Attendance at conferences should also be documented but in this case, the date and title of the conference is usually all that can be recorded. It may be beneficial to include a copy of the programme, although in the case of the larger conferences this is not always practical. A list should be kept of all formal in-house training received, again with dates and the title of the training, including a list of SOPs the employee has been trained in, including the appropriate version numbers. Ideally, the signature of the person giving the training should confirm attendance. Where on-the-job training has been given in association with another member of the department, the date and the details of the particular task taking place should be recorded. The accompanying member of the department should sign and confirm whether the trainee was merely observing or was being supervised on completing the task. As has been mentioned earlier, once the trainee is considered to be sufficiently capable of performing any given task alone, a certificate of competence should be prepared and signed by the departmental manager.

The maintenance of the training record is the responsibility of each individual and it is his/her responsibility to ensure that it is kept up-to-date at all times. In this way, all personnel should be able to readily confirm that they are qualified through education, training and experience to perform the tasks that they are undertaking. Compliance with the requirements of the GXP's can thus be demonstrated to the satisfaction of any inspector or auditor.

# Integrating Quality Systems

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Over the decades, applying certain quality principles and standards to the development, manufacture, distribution and servicing of products has become the norm. The first set of principles was established as the International Standards Organisation (ISO) series. However, different industry types have since customised these principles mainly *via* the addition of further interpretative details for their particular industry. We now have, for example, the GXP for regulatory work, OHSAS 18001 for Health and Safety at Work, ISO 14001 for environmental care, *etc.* Much similarity can be seen if one looks carefully at the core principles of these standards.

Quality means a standard. As worldwide competition develops in a “global village”, there are no products on the market today which do not meet the respective requirements of their particular industry. As in the pharmaceutical, biotechnology, consumer products and medical device industries (The Industry) and related fields such as diagnostics, the drive for quality is at the forefront of product development, manufacture and distribution.

In this respect, the above industries are reverting to a historical quality management model, where the quality of the product was dictated by those responsible for its manufacture rather than testing the quality or trying to assure that the quality was “built-in” by preventive work practices.

This “historical” concept has led to focussing more on the product and less on the surrounding services of QC and QA. By ensuring the product pathway is focussed on devising, developing and manufacturing products which are likely to meet consumer demand (or generated demand) there is greater assurance of success. This means that we can show competence and compliance in the development of quality management and quality management systems.

Where to start? Problems companies may face are when to implement a QMS or, in the case of established companies, how to integrate diverse systems or divisions following acquisition or merger. Thus difficulty can be compounded by poor management and change control mechanisms, resulting in poorly informed, reticent staff. The purpose of the following is to define the requirement of various quality systems, and offer guidance on when and how they could be implemented.

It is not the intention of this chapter to review the GXP and other standards. That has been covered eloquently by previous authors. However, an overview of the role of each standard may be useful (Appendix 1 to this chapter: Standards, definitions and areas of use).

## 40.1 HISTORY AND OBJECTIVES OF THE STANDARDS

The ISO 9000 series was developed to break down international barriers to world trade. Theoretically, an organisation that can demonstrably meet the requirements of ISO 9000:2000 is producing a product that meets customer requirements, appropriate technical requirements and any

additional legal obligations to the same standard as other organisations adopting ISO 9000:2000 anywhere else in the world. Thus, any trade barriers arising from cultural or political issues are minimised. The aim of this standard is also to encourage continuous improvement and success for the organisation. ISO compliance is assessed by profit-making accreditation bodies.

GLP, GCP and GMP (GXP) were introduced to prevent fraud, protect the consumers as well as the integrity of data submitted to regulatory agencies for drug or product marketing permits. For example, GLP is a legal requirement for the pre-clinical (mainly safety) testing of new drugs, novel consumer products and ingredients. Test items must be thoroughly studied to ensure that they are safe for consumption and exposure to the environment. The recipients of the regulatory submission (study reports) are the regulatory agencies, but clearly the consumers of the new drugs or products (end-user) are the beneficiaries of the work that went into the submission. For organisations contracted to undertake this work on the behalf of a sponsor, the sponsor is also a customer. Currently GXP compliance is assessed by non-profit-making government organisations.

ISO 17025 is very similar to ISO 9000:2000, the general quality management standard, but is specifically designed for testing and measurement laboratories or service organisations. Elements of this standard encourage technical competency, accuracy and precision.

ISO 14001 is primarily designed to minimise impact of operations on the environment. Organisations are expected to adopt eco-efficient practices and can save money as a result. Multi-national organisations implementing the standard wisely may save hundreds of millions of dollars over the medium term (*e.g.* 5 years). In return, their contribution to global pollution is reduced, thereby helping us to preserve the environment. Multi-national companies are increasingly becoming aware of their impact on the global environment and that to become sustainable industries they must be fully committed to addressing these issues. The customer in this respect is society as well as the organisation itself.

The Occupational Health and Safety Assessment Series 18001(OHSAS 18001) aims to help minimise employee exposure to occupational health and safety hazards. This standard also helps organisations to comply with statutory health and safety legislations. OHSAS is applicable to any kind of organisation, the customer being the employee.

Many organisations may have a need (legal or voluntary) to implement two or more of the above standards when an appreciation of the similarities and differences between the standards is crucial to their effective harmonisation.

The ISO and GXP standards vary in two major aspects. Unlike the GXPs, the ISO standards have not been devised for use in a single industry. While apparent inconsistencies may be of concern to those who wish to maintain differentiation between the various standards, particularly the GXPs, these do not prevent pro-active organisations from combining systems while retaining regulatory and business compliance requirements. The secret of business success is to meet the requirement of the most comprehensive standard. Appendix 2 to this chapter compares the various standards.

## 40.2 BENEFITS OF AN INTEGRATED QUALITY MANAGEMENT SYSTEM

The benefits to implementing a single quality management system based on two or more standards include simplification and optimal use of resources. Today's business environment is becoming increasingly competitive. Large organisations usually derive improvements in efficiency *via* budget cuts; the first areas to be scrutinised are generally those relating to infrastructure, including quality management, especially where duplication excels, *e.g.* between research and production.

In these cases it is likely that the following functional elements relating to quality management would be evaluated for rationalisation and added value to the organisation:

- Quality Assurance (QA)
- Quality control



- Documentation control
- Records management (*e.g.* archives and document stores)
- Operational areas (*e.g.* shared laboratories for GXP and non-GXP work, laboratory services)
- Reporting processes
- Computer support
- Organisational structure (due to rationalisation of functional and operational areas).

### 40.3 CHALLENGE OF IMPLEMENTING AN INTEGRATED MANAGEMENT SYSTEM

Implications of the above rationalisations are mainly “people related”, and effective “change management” processes become a significant factor for successful implementation of an integrated management system. For most people involved, implementing an integrated quality management system will pose a threat to their security, comfort zones and in some cases personal empires. Strong emotional ties are commonly the cause of resistance to change. There will also be cost implications as staff will need to acquire extra skills and competencies, and this will take time and training. Auditors would need to be knowledgeable in more than one quality standard and in the interpretation and implementation with respect to integration (see Section 40.16 for more).

Cost is also associated with amalgamating controlled documentation, such as policies and procedures. It is possible that the organisation has more than one set of controlled documentation for communicating the quality management system and procedures arising from the separate quality standards. For global organisations there will undoubtedly be further cultural and communication difficulties.

### 40.4 AN INTEGRATED QUALITY MANAGEMENT SYSTEM

The following considers the content of a quality manual for an integrated quality management system meeting the requirements of the stated standards. Since ISO 9001:2000 offers the least prescriptive recommendations, the following sections are structured around the major clauses of this standard.

### 40.5 MANAGEMENT RESPONSIBILITY

Management responsibility is at the core of all quality management standards. Without high standards of leadership and direction, people management and a focus on customers, an organisation is unlikely to be sustainable. Current research is demonstrating that the key elements of successful organisations are effective leadership. For long-term sustainability these are driven by a carefully researched and developed policy and strategy, well-managed resources, productive partnerships with suppliers and carefully designed, reviewed and improved processes. Leaders should also frequently monitor performance and key results to identify areas for the purposes of learning and continuous improvement.

When considering an integrated quality management system, the above attributes can easily be identified for most standards, particularly those related to ISO 9000:2000; the recipients or entities purchasing the products are clearly the customers. The GXP standards are less clear on the identity of the customer, organisational improvement, people development and performance monitoring. Thus for an organisation requiring to establish an integrated management responsibility policy, it is important to understand the history and objectives behind the original development of the standards themselves, to identify the “hidden customer”.

For all the quality standards, people’s roles and responsibilities must be clearly defined and documented as well as the reporting lines. All the quality standards highlight the need for adequate



staff, technical and financial resources to be provided together with clear accountability and responsibility.

The ISO-based standards include a clause that specifies an organisation must comply with any legal obligations and these would override conflicts, if any, with the ISO standard.

In addition to the basic ISO 9001:2000 framework, ISO14001 requires that measurable environmental objectives and targets are set with a management programme with timeframe to ensure the targets are met.

## 40.6 POLICY STATEMENTS

For the ISO related standards, a clear policy geared towards meeting the needs and expectations of customers is required, such as that exemplified by Appendix 3 to this chapter. Declarations of conformance to the individual standards are also important. Mission and quality policy statements would need to refer to the legal obligations in relation to regulatory submissions, care for the environment and occupational health and safety requirements. Consumer needs could also be stated where they may be indirect beneficiaries of the product.

The policy statement should include a clear commitment by Management to implement, comply with and sustain compliance with the standards. Management should also commit to communicate the obligations of the standards to all employees, clients and suppliers. It is a legal requirement for companies to publish H&SAW policies.

Risk assessments are a key and unique feature of OHSAS 18001 (see latter sections). In addition, occupational health and safety issues are also required to be addressed for the GXPs in order that accidents or personal health problems arising from work do not affect the integrity of studies, or put manufactured products at risk. This area will gain in prevalence as “hidden diseases” such as HIV become more endemic, particularly in those areas where the future generics market is growing. Based on this premise, it is consistent to include health and safety as an integral part of a QMS for this industry. The H&SAW policy could be extended therefore to embrace GXP requirements.

Commitment to improvement is also a significant statement that should be made in the quality policy. Although not explicit for the GXPs, audit and corrective action implies that some form of continuous improvement occurs.

The GXPs do not specify management commitment, management review, customer focus or the need for a quality policy. However, addressing these aspects would certainly add value to GXP organisations. In practice they are quite frequently addressed in the form of GXP policies and management forums that meet to discuss quality issues.

ISO 14001 requires that the policy reflects the nature, scale and environmental impacts of its products or services such as a commitment to preventing pollution.

## 40.7 RISK ASSESSMENTS

Unlike GXPs and ISO 17025, OHSAS states that risk assessments should be carried out. Hazards should be identified, risks assessed and control measures developed and implemented. The GXP standards require health and safety procedures to be followed to protect the study participants and hence the integrity of the study, but GXP auditors are not expected to audit for health and safety requirements.

ISO 9000:2000 states that management of risk should be addressed, for example, with respect to change control and safety. ISO 14001 requires a preparatory review and definition of an organisation's impact on the environment in order to develop a programme of work and measurements. Apart from the GXPs, therefore, risk assessments of varying types are required. GXP environments could benefit from risk assessments on major changes to the organisation or processes.

Crisis, incident or emergency management are also addressed by OSHAS 18001 and ISO 14001. Product recall is an integral component of GMP and management of adverse events is a

requirement of GCP. Although managing emergencies is not mentioned in the other standards, they would certainly benefit most organisations for some aspect of their operation or service. For example, it would be a wise organisation that had procedures in place to minimise the impact both to the consumer and to the business in the event of a marketed product, such as a cosmetic, food or pharmaceutical getting contaminated with the potential to cause harmful effects (remember Perrier!).

#### **40.8 MANAGEMENT REVIEW**

For the ISO-based standards and OHSAS18001, management review clauses are essentially the same but in the GXP they take the form only of audit report sign-off with no other forum required for overall management review of a GXP facility. There is potential for the management review approach to add value to a GXP environment as it would incorporate a performance review against stated delivery with requirements for continuous improvement purposes and ensuring customer expectations are met.

#### **40.9 MANAGEMENT REPRESENTATIVE**

For ISO 9000-based standards a management representative is required to be appointed to ensure the effective implementation of the quality system. For GXP facilities management (as defined in documentation) is responsible for implementation of the quality system. These roles and responsibilities are not dissimilar. However, for the ISO-based standards, the management representative also has a responsibility to ensure that an effective, independent audit programme is established. For the GXPs, this responsibility lies with the QA function that is independent of study or production management. In practice, GXP QA advise management on interpretation of quality standards and hence development, maintenance and improvement of a quality system.

#### **40.10 RESOURCE MANAGEMENT**

For any quality system, the provision of adequate facilities, competent people, equipment, consumables, *etc.*, is fundamental to organisational performance. Management must provide these. Systems for assessing future resource needs must be established and this is where effective strategy development or planning becomes important. These aspects are best addressed by ISO 9001:2000 and OHSAS management models. GCP does not adequately cover resources. GCP requires that the study monitor (essentially a management representative) ensures that resources are available to the study investigator (supplier). GLP and GMP do address resource management by specifying that management must be responsible for the adequate provision of resources. For GLP this can be monitored *via* the Master Schedule. However, OHSAS and ISO 9000:2000 go a step further and provide a basic model whereby the organisation is expected to consider its overall performance, and audit report findings for its planning process.

#### **40.11 SUPPLIER MANAGEMENT**

This aspect is addressed by all the standards. Sub-contracting must be carefully monitored for GXP and fairly intensive supplier audits conducted, particularly for GCP studies outsourced to investigator sites with no established quality systems in place. For the ISO standards the supplier management clause applies to critical suppliers and is, therefore, entirely compatible with the GXPs.

#### **40.12 PRODUCT REALISATION/PROCESS MANAGEMENT**

Processes for making the product or delivering a service must be defined for all quality standards. It is also important that processes, where possible, are tested and validated for effectiveness and

reliability. However, the degree of detail varies according to the standards adopted, the complexity of the operations and the demonstrated competency of the operators. The GXPs generally apply to highly technical research-based environments, and process descriptions comprise part of the legal data trail required to demonstrate integrity. While ISO 9001 specifies a requirement for product realisation plans, the GXPs are far more specific in that the general content of study plans, clinical protocols and production batch records are stated. For ISO 14001 an environmental management programme with timeframe must be deployed to ensure that set targets are met. In some ways this could be analogous to a GXP study or batch production run. An environmental report must be produced and used as the basis for improvement. The production of this report will probably be based on the measurement, collation and analysis of data pertaining to environmental factors.

The standards ISO 14001, ISO 17025 and OSHAS 18001, therefore, demand the same but with a degree more detail than the GXPs,

### 40.13 CONTROLLED DOCUMENTATION SYSTEM

One of the key elements of any QMS/GXP system is documentation, and associated change control mechanism to ensure that current documentation is used. A common feature of the GXPs and the ISO series is the use of valid procedures.

To meet this requirement, all the above systems require an approval process by management to ensure that documents are authorised at the required level and a review mechanism to ensure documents follow current best practice available at the time of review. A version control mechanism must be used to allow traceability of the procedure in use at a specific time-point, thus allowing reconstruction in conjunction with the records from that period.

For an integrated system the ISO 9001:2000 standard defines the requirements necessary to fulfil the GXP regulatory requirement as well as the more relaxed ISO standards. The crucial factor is the maintenance of the change control mechanism, using a risk assessment of the likely change and validation of the proposed change prior to introduction. Any change is expected to rationalise, maintain or enhance business practice, quality or safety. The change should only be introduced where it is not detrimental to the other areas.

In any GXP or QMS there are five general categories of documentation: Procedures (SOPs), protocols (study plans), reports, batch-related documents and test records. All are subject to a review mechanism based on the differing function of the document. An SOP would normally be reviewed on a routine basis (*e.g.* once in 2 years), a protocol/report at the beginning/end of a project, while a batch record would be reviewed based on development/validation work or production of previous batches. The variation in time of review is the only significant difference and there is no reason for not using a single control mechanism for all documentation and records.

For each issue of a document the minimum requirement is as follows (see Chapter 36):

Document Code	Title	Mgmt /QA Approval	Version No.	Issue Date	Replacement Date	Reason for change	Communicated to:
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There is a general acceptance that QA review is a necessary requirement for both regulatory function and meeting and improving quality targets within organisations. The QA review of documentation is expected in the GXPs, although some companies in GLP are moving towards an author/manager sign-off, and excluding QA from the formal review/sign-off process. This is a question of balancing available resources against risks to compliance. The QA review of documentation is recommended as it promotes quality and consistency throughout a company by ensuring a consistent, independent approach regardless of specialist area.

#### 40.14 RECORDS AND DATA GENERATION, RETENTION AND PROTECTION

Records, especially where these are generated electronically, should be the simplest area to harmonise across disciplines. The generation of records gives the greatest risk of non-conformance/non-compliance across all standards because

- Records are the variable in any QMS whereas documentation is, or should be, defined and controlled.
- Records are generated directly (or indirectly for some electronic records) by humans.

The basic concept should be that the records are legible, indelible (permanent) and correct. Most of the standards have this as a stated requirement. There is also a need to ensure that if the data are changed there is traceability to the original entry and a documented reason for the change provided. Retention and security of data are simpler for original paper data, mainly due to the requirement to retain the records in a stated location for a requisite period of time. This becomes increasingly difficult for electronic records due to the ability to transmit these to a variety of locations, disciplines and time zones at a single keystroke (almost).

The key to successful paper or electronic data collection in any QMS is to limit the collection to a minimum, control data collected using templates (such as Authorised Forms) and reduce the manipulations required to obtain the result to be reported.

Protection of records, using back-up and archive procedures, is becoming a standard requirement throughout the GXP industries, with paper, as well as electronic records, being held as originals and authenticated copies.

Electronic records in all disciplines should be "...trustworthy, reliable and generally equivalent to paper records and handwritten signatures executed on paper" (21CFR11; US FDA). To achieve this, e-records should be "...created, modified, maintained, archived, retrieved or transmitted..." to meet the standard set by their paper equivalents. The requirement to achieve this across the GXPs may be one of the greatest harmonisation tools that companies can use to implement integration strategies. The requirement across the GXPs is the same for registration data, and should ensure that a consistent approach is used. As a by-product of its intended purpose, the above legislation may promote a cross-discipline/standard environment which promotes quality in more than just data.

#### 40.15 PEOPLE MANAGEMENT

There is a clear requirement in all the standards discussed to ensure that competent personnel are used for the correct function. Companies should define personnel structure and requirements prior to initiation or change of company structure. A clear, current and proposed staff structure diagram should be in place to show management and responsibilities of personnel. This can be multi-layered, breaking down each area by management, with sub-layers showing individual personnel. A visual diagram aids explaining often-complex relationships in a simple flow sheet. In the same way that a product requires a specification, each post within the organisation should be clearly described, and include the responsibilities of the post. By stating the requirements prior to recruitment, the post is filled and not "created" for the applicant.

Each member of personnel should have at least the following paper or electronic records:

- Curriculum vitae (CV)
- Job description, including responsibilities
- Training record, including assessment/sign-off of competence in required tasks
- Certification of internal/external courses
- Future training requirement (usually based on a personal performance review).

Various electronic and paper-based human resource management tools exist to assist in the implementation. While the documentation requirements seem extensive, most will be available in some format for most companies.

The most important criterion for ensuring quality in any integrated system is selection of the correct personnel for the role(s). Too much resource is wasted pruning square pegs for round holes. Selection of personnel should consider the mental and physical requirements of the post, the nature of the job (skills and competencies) and, most importantly, ability to implement and support work practices involving more than one standard. If personnel will not move from the “comfort zone” of working within a single standard, the company faces an insurmountable challenge to the integration process.

## **40.16 INTEGRATED QUALITY ASSURANCE (INTERNAL AND THIRD PARTY)**

### **40.16.1 General Considerations**

The role of QA staff could be of a QC checker, police force, a pre-emptive trainer/mentor or a team player. This spectrum of activity is seen between all standards and is a reflection of management commitment and knowledge rather than the designated role of QA in any particular discipline. The basic function of QA is to provide an independent assessment to organisation management on the function and performance of the QMS, regardless of discipline(s) involved.

The use of QA personnel across disciplines (super-auditors) requires more extensive training than it does for current GXP, where terminology varies for roles, *e.g.* investigator (GCP) *vs.* Principal Investigator (GLP). Systems using general terminology removes “mystique” and allows QA inspection to concentrate on the reconciliation of procedure against data collected. An interim measure should be the cross-training between different disciplines and check lists which reference common areas/different jargon across the standards. The use of ISO terminology with a GXP Glossary may be useful.

### **40.16.2 Monitoring Programme**

Unless multiple products are under development, the sequence of QA activity tends to be as follows: Research and Development (ISO 9001 is useful), GLP for Safety, GMP-type manufacture for use in GCP clinical trials, and GMP for manufacturing following authorisation. Few organisations encompass all three disciplines at the same time, or within the same organisation structure. Where multiple disciplines are performed, the QA monitoring programme can use ISO guidelines to assist in formulating auditing, inspections and project management schedules.

Monitoring is required for internal, off-site and third-party work. Internal and off-site work, carried out within another part of the organisation can be treated as part of the internal QMS environment, regardless of the discipline. Some companies will use the “Approved Supplier” ISO system for different parts of an organisation that are capable of providing the same service. This improves efficiency and cost-effective supply. External (third-party) agencies, such as contract research or contract manufacturing organisations (CROs and CMOs) can be dealt with using the ISO “Approved Supplier” system, with pre-approval inspection and on-going liaison/inspection with the supplier at agreed intervals. The mechanism for appointing approved suppliers in ISO has several options (*e.g.* “historical” supply) which do not meet the requirements of GXP although the use of ISO 9001-registered suppliers should allow more awareness of the supplier’s capabilities.

### **40.16.3 Pre-emptive Action**

Assessment of competence, by validation or other mechanisms, is the most common form of error reduction. The design/validation component of ISO 9001:2000 complements the IQ/OQ/PQ system in general use in the pharmaceutical and related industries (see Chapter 21 Section 21.4.1). The involvement of QA in the validation/training process can act as a brake on progress, and is not always defined as a requirement.

All personnel should be encouraged to implement and support pre-emptive action, with emphasis on error/waste prevention rather than cure. This is a cultural requirement of the ISO QMS system, but not clearly defined in the GXPs. Integrated systems should place more emphasis on the validation/prevention role rather than a find-and-correct role.

#### **40.16.4 Corrective Action**

Find and Correct: The GXP QA policeman role is endemic throughout the GXP family. The majority of QA effort is at the report/batch review stage rather than in the pre-emptive/quality improvement area. Multi-discipline systems must ensure that the corrective action implemented is carried across disciplines, with the recall of defective investigational products (IP's) being a good example. It is essential that all corrective actions are assessed for completion and closeout. There should be a documented review of prevention of recurrence.

#### **40.16.5 Preventive Action**

Preventive action based on quality improvement is a self-assessment or external response simulation which prompts the organisation to assess defects and error and implement change to try to prevent recurrence. The industries involved in the GXP standards have a poor record on preventative action, particularly as information is not readily shared throughout the industry. All corrective actions by QA or management should include a preventive assessment, even if limited in scope. Current QA GXP documentation can be easily adopted for this purpose. It is essential that management endorsement of preventive action be obtained to lend authority to the process change.

### **40.17 QUALITY CONTROL? QUALITY CHECK!**

Quality control is often mistaken for Quality Assurance. Quality control (QC) is a technical process, where the inputs (raw materials) into a process (such as production), and the expected outputs (the product) are monitored to determine if they meet designated criteria.

Quality control is well defined in all sections of the ISO 9000:2000 standard to ensure that raw materials, process design, in-process controls and monitoring at various stages are clearly defined.

Quality control should be seen as confirmation of pre-defined criteria rather than being used as the confirmation that a product or test is fit for use. This can only be implemented where the QMS is capable of ensuring that quality is built in to the testing or production process. In some areas, including manufacture of early-phase clinical trials material, there is a greater reliance on QC to ensure quality due to the lack of information surrounding new entities (see Chapter 29). The development of GMP/GCP regulations should assist in establishing greater control over the test product, and lessen QC input.

### **40.18 HOLISTIC BUSINESS EXCELLENCE MODELS**

Holistic total quality business models such as Malcolm Baldrige and the European Foundation for Quality Management (EFQM) excellence models are growing in popularity and have been proven to enhance business success. They generally address the following aspects:

- Leadership
- Strategy
- Processes
- Partners and suppliers
- People
- Organisational results.



The EFQM model strongly advocates checking for linkages between approaches (*i.e.* strategies and processes) to results for continuous review of organisational performance to enhance learning and improvement. ISO 9001:2000 is heavily based on the EFQM model and commonly forms the core management system for organisations implementing holistic business excellence models.

It is possible to find organisations integrating quality standards (especially ISO 9000:2000 and ISO 14001) and other management tools such as the HAX Strategy development process and balanced score cards under these headings to make them work cohesively in favour of the organisation, its people, society, customers and stakeholders. Ethical business practices and sustainability *via* care for the environment are also the key to these holistic business models and, therefore, clearly complementary to the GXPs.

### Appendix 1 Standards, Definitions and areas of use

<i>Standard</i>	<i>Status</i>	<i>Area of use</i>
Good manufacturing practice	Regulatory requirement	Manufacture of pharmaceutical and related products (2003–2004) Manufacture of clinical products
Good laboratory practice	Regulatory requirement	Safety testing of prospective products
Good clinical practice (Human and Vet)	Guideline (2002) Regulatory requirement (2004+?)	Clinical (efficacy) testing of material
ISO 9000	Guideline	Quality Management System (QMS): General principles for all business activities
ISO 14001	Guideline	QMS for assuring acceptable environmental conditions in business
OHSAS 18001	Guideline	QMS for health and safety

### Appendix 2 How the standards compare for basic requirements of a QMS

<i>Standard</i>	<i>ISO 9000</i>	<i>GMP</i>	<i>GLP</i>	<i>GCP</i>	<i>ISO 17025</i>	<i>ISO 14001</i>	<i>OSHAS 18001</i>
Section							
Management	3	3	2	1	3	3	3
Validation	2	3	1	1	3	2	1
Documentation	2	3	2	3	3	2	2
Records and data	2	2	2	2	3	3	3
Training	2	2	2	2	3	2	2
QA	3	1	3	1	2	2	3
IT	1	1	1	1	1	1	1
Continuous improvement	3	1	1	1	1	3	3
Total	18	16	14	12	19	18	18

*Note:* 3 indicates comprehensively covered; 2 addressed; and 1 alluded to (not explicit).



**Appendix 3** *Example policy Statement*

The objectives of the company are:

- To ensure the highest possible level of client satisfaction
- To ensure ethical and profitable business relationships are initiated and expanded
- To ensure that personnel achieve personal satisfaction in their work
- To care for the environment and promote sustainability
- To ensure new products are safe for the consumer.

This will be achieved by:

- Commitment from management to maintain and improve business processes
- Ensuring that all personnel understand the policy and conform to defined procedures
- Requiring all personnel to be responsible for the quality of their actions and ensure that the products provided conform to the relevant quality standards
- Compliance with regulations and guidelines for Good Laboratory Practice for the safety testing of our products
- Compliance with regulations and guidelines for Good Clinical Practice, to assess the efficacy of our products
- Compliance with regulations and guidelines for Good Manufacturing Practice to ensure the quality during manufacture and distribution of our products
- Compliance with ISO 14001 (Environmental Management standard)
- Compliance with OSHAS 18001
- Encouraging all personnel to seek continuous quality improvement
- Review by Management of the Quality Objectives on a routine basis.

These objectives will be attained by commitment to the principles defined in the Quality Management System, which are found in the procedures used for the normal work practices within this company.

Signed..... Date.....

Managing Director and Senior Manager



# Glossary of Some Commonly-used Abbreviations

P. CARSON AND N. DENT

ABHI	Association of British Healthcare Industries
ABPI	Association of the British Pharmaceutical Industry
ACNFP	Advisory Committee on Novel Foods and Processes
ACRE	Advisory Committee on Releases to the Environment
ACRPI	Association of Clinical Research for the Pharmaceutical Industry
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AE	Adverse Event
AFR	Annual Financial Return
AHPPI	Association of Human Pharmacologists in the Pharmacological Industry
AIM	Association of Independent Multifunds
AIOPI	Association of Information Officers of the Pharmaceutical Industry
AMA	American Medical Association
ANDA	Abbreviated New Drug Application (for approval to market a generic drug)
AMRIC	Animals in Medical Research Information Centre (part of the ABPI)
ANDs	Abbreviated New Drug Submissions
ANSP	Annual Selling Price
AOSA	Association of Official Seed Analysts
AOSCA	Association of Official Seed Certifying Agencies
APG	American Pharmaceutical Group
API	Active Pharmaceutical Ingredient
API	Association of Parallel Importers
AREC	Association of Research Ethics Committees
ARSAC	Administration of Radioactive Substances Advisory Committee
ATCs	Anatomical Therapeutic Chemicals
BAEPD	British Association of European Pharmaceutical Distributors
BAPW	British Association of Pharmaceutical Wholesalers
BARQA	British Association of Research Quality Assurance
BCPC	British Crop Protection Council
BEMA	British Essence Manufacturers' Association
BfArM	German Federal Institute for Drugs and Medical Devices
BIA	Bio-Industry Association
bid	Twice Daily
BIO	US Biotechnology Industry Organisation
BGMA	British Generic Manufacturers Association

BIA	Bio-Industry Association
BHJ	British Hospital Journal
BINAS	Biosafety Information Network and Advisory Service
BIRA	British Institute of Regulatory Affairs
BIVDA	British In vitro Diagnostics Association
BMA	British Medical Association
BMJ	British Medical Journal
BP	British Pharmacopoeia
BPG	British Pharma Group
BPI	British Pharmaceutical Index
BPMRG	British Pharmaceutical Market Research Group
BrAPP	British Association of Pharmaceutical Physicians
BSE	Bovine Spongiform Encephalopathy
BSI	British Standards Institution
BVA	British Veterinary Association
CA	Clinical Assistant
CADREAC	Collaboration Agreement of the Drug Regulatory Authorities of the EU Associated Countries
CAR	Corrective Action Report
CAP	College of American Pathologists
CBA	Cost Benefit Analysis
CBI	Confederation of British Industry
CBD	Convention on Biological Diversity
CHM	Clearing House Mechanism
CDER	Centre for Drug Evaluation and Research
CEBM	Centre for Evidence-Based Medicine
CEN	Comite' Europe'en de Normalisation
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CG	Clinical Governance
CGIAR/SINGER	System-Wide Information Network for Genetic Purposes
CGMP	Current Good Manufacturing Practice
CHD	Coronary Heart Disease
CHI	Commission for Health Improvement
CHMP	Committee for Human Medicinal Products
CI	Continuous Improvement
CIOMS	Council for International Organisations of Medical Sciences
CIPA	Chartered Institute of Patent Agents
CJD	Creutzfeldt-Jakob Disease
CLA	Copyright Licensing Agency
CMC	Chemistry, Manufacturing and Controls
CME	Continuing Medical Education
CMRI	Centre for Medicines Research International (Part of the ABPI)
CMS	Concerned Member State
CNS	Central Nervous System
C of A	Certificate of Analysis
COC	Combined Oral Contraceptive
COG	Cost Of Goods
COMP	Committee on Orphan Medicinal Products

CoP	Code of Practice (see PMCPA)
COREC	Central Office for Research Ethics Committees
COS	Clinical Overall Summary
CPA	Clinical Pathology Accreditation (UK Ltd)
CPMP	See CHMP (name change in line with Directive 75/319/EEC)
CPSM	Council for Professions Supplementary to Medicine
CPVO	Community Plant Variety Office
CRA	Clinical Research Associate (or Monitor)
CRC	Clinical Research Council
CRD	NHS Centre for Reviews and Dissemination
CRE	Clinical Research Executive
CRF	Case Report Form
CRO	Contract Research Organisation
CTD	Clinical Trials Directive
CTPA	Cosmetics, Toiletries, and perfumery Association
CSM	Committee on Safety of Medicines
CTC	Clinical Trial Certificate
CTD	Common Technical Document
CTX	Clinical Trial Exemption Certificate
CV	Curriculum Vitae
CV	Cardio Vascular
CVMP	Committee for Veterinary Medicinal Products
CCU	Coronary Care Unit
DDD	Defined Daily Dose
DDMAC	Division of Drug Marketing Advertising and Communication
DDX	Doctors and Dentists Exemption Certificate
DEFRA	Department for the Environment, Food and Rural Affairs (UK)
DIC	Drug Information Committee
DIP	Drug Information Pharmacist
DLT	Drug Limiting Toxicity
DMF	Drug Master File
DMRC	Defective Medicines Report Center
DNA	Deoxyribonucleic Acid
DoH	Department of Health (UK)
DphO	District Pharmaceutical Officer
DQ	Design Qualification
DSMC	Data Safety Monitoring Committee
DSRU	Drug Safety Research Unit
DTC	Direct to Consumer
DTI	Department of Trade and Industry
DUMP	Disposal of Unwanted Medicines and Poisons
EAEPC	European Association of Euro-Pharmaceutical Companies (Parallel Traders)
EBM	Evidence-Based Medicine
EC	European Commission
EC	European Community (Superseded by EU)
ECP/GR	European Co-operative Programme for Crop Genetic Resources Networks
EDMA	European Diagnostic Manufacturers Association
EDQM	European Dept for the Quality of Medicines

EEA	European Economic Area
EFB	European Federation of Biotechnology
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries & Associations
EFTA	European Free Trade Area
EGA	European Generic medicines Association
EIR	Establishment Inspection Report (FDA visit report)
EL	Executive Letter (from NHSE)
EMC	Electronic Medicines Compendium (from ABPI)
EMA	European Medicines Evaluation Agency
EMIG	Ethical Medicines Industry Group
ENT	Ear, Nose and Throat
EPA	Environmental Protection Agency (USA)
EPC	European Patent Convention
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organisation
EQA	External Quality Assessment
ERG	Ethics Review Group (see IEC and IRB)
ERPG	Eastern Region Pharmaceutical Group
ETMS	Electronic Territory Management System
EU	European Union
EUFIC	European Food Information Council
EURO	European Currency Unit
EuropaBIO	European Association for Bioindustries
FAO	Seed and Plant Genetic Resources Service
FAO/	Global Plant and Pest Information System
FDA	Food & Drug Administration (US Licensing Authority)
FDA 483	FDA form used for reporting Inspection Observations
FDA1572	FDA form used as Statement of Investigator
FEBC	Forum for European BioIndustry Co-ordination
FIFRA	The Federal Insecticide, Fungicide and Rodenticide Act (USA)
FFDCA	Federal Food, Drug and Cosmetic Act (USA)
FOI	Freedom Of Information
FPA	Family Planning Association
FPC	Family Planning Clinic
FP10	Prescription Form
FPM	Faculty of Pharmaceutical Medicine
FQPA	Food Quality Protection Act
FSC	Free Sale Certificate
FTC	Federal Trade Commission
ftp	File Transfer Protocol (Internet)
GALP	Good Automated Laboratory Practice
GAMP	Good Automated Manufacturing Practice
GATT	General Agreement of Tariffs and Trade
GCP	Good Clinical Practice
GCPF	Global Crop Protection Federation
GDP	Good Distribution Practice
GEF	Global Environment Facility

GI	Gastro Intestinal
GIBiP	Green Industry Biotechnology Platform
GIRP	European Pharmaceutical Wholesalers Federation
GLP	Good Laboratory Practice
GM	Genetically Modified
GMC	General Medical Council
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GNP	Gross National Product
GPIA	Generic Pharmaceutical Industry Association
GPC	General Practitioners Committee (part of BMA)
GPCG	General Practitioners Research Database
GRPD	General Practice Research Database
GSL	General State List ( <i>i.e.</i> of medicines available on sale without prescription)
GTAC	Gene Therapy Advisory Clinic
HA	Health Authority (Health Boards in Scotland)
HAAG	Healthcare Advertising Agencies Group
HACCP	Hazard Analysis Critical Control Points
HAI	Health Action International
HAZ	Health Action Zone
HC	Health Commission
HCP	Health Care Professional
HEA	Health Education Authority
HGAC	Human Genetics Advisory Committee
HGP	Human Genome Project
HImPs	Health Improvement Programme
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organisation
HPC	Health Professions Council
HR	Human Resources
HRT	Hormone Replacement Therapy
HSMC	Health Services Management Centre
HTA	Health Technology Assessment
HUGO	Human Genome Organisation
IAFN	International Agri-Food Network
IAMA	International Food and Agribusiness Management Association
IB	Investigator's Brochure
ICA	International Co-operative Alliance
ICC	International Chamber of Commerce
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICH	International Conference on Harmonisation
ID	Identification (Patient)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IEC	International Electrotechnical Commission
IFA	International Fertiliser Industry Association
IFAP	International Federation of Agricultural Products
IFIC	Institute of Food Technologists



IFPMA	International Federation of Pharmaceutical Manufacturers Association
IHSM	Institute of Health Services Management
ICU	Intensive Care Unit
IIP	Investors in People
IISD	International Institute for Sustainable Development
IMA	Independent Medical Advisor
IMB	Irish Medicines Board
IMPs	Investigational Medicinal Products
IMS	Intercontinental Medical Statistics
IND	Investigational New Drug
IQ	Installation Qualification
IQA	Internal Quality Control
IRB	Institutional Review Board
InVIVO	In Life
InVITRO	In Test Tube
IP	Intellectual Property
IPA	Indicative Prescribing Amount
IPGRI	International Plant Genetic Resources Institute
IPHA	Irish Pharmaceutical Healthcare Association
IPP	Intellectual Property Protection
IPR	Intellectual Property Rights
IQ	Installation Qualification
IR	Investor Relations
IRB	Institutional Review Board
IRCA	International Register of Certification Auditors
ISAAA	International Service for the Acquisition of Agri-Biotech Applications
ISEB	International Society for Environment Biotechnology
ISO	International Standards Organisation
ISTA	International Seed Testing Association
ISTAHC	International Society of Technology Assessment in Healthcare
IU	International Unit
IVF	In vitro Fertilisation
IV	Intravenous
JAMA	Journal of the American Medical Association
JD	Job Description
LAL	Limulus Amoebocyte Lysate
LAN	Local Area Network
LCA	Local Care Agency
LHC	Local Health Care Co-operative
LHG	Local Health Group
LIMS	Laboratory Information Management System
LMC	Local Medical Committee
LMCA	Long-Term Medical Conditions Alliance
LREC	Local Research Ethics Committee
LTVPG	London and Thames Valley Pharmaceutical Group
MA	Medical Advisor
MA	Marketing Authorisation

MAL	Medicines Act Leaflet
MAT	Moving Annual Total
MBO	Management by Objectives
MCA	Medicines Control Agency (UK)
MCO	Managed Care Organisation
MD	Doctor of Medicine
MDA	Medical Devices Agency
MDI	Medical Data Index
MDI	Metered Dose Inhaler
MDU	Medical Defence Union
MedDRA	Medical Dictionary for Regulatory Activities
MeReC	Medicines Resource Centre (now part of the National Prescribing Centre)
MHPRA	Medicines and Healthcare Products Regulatory Agency
MHUCT	Medicines for Human Use (Clinical Trials) Regulations
MI	Myocardial Infarction
MIMS	Monthly Index of Medical Specialities
MLA	Medical Laboratory Assistant
MLSO	Medical Laboratory Scientific Officer
MMR	Measles, Mumps, Rubella Combined Vaccine
MOH	Ministry of Health
MPA	Medical Products Agency, Sweden
MPI	Medical Pharmaceutical Index
MRA	Mutual Recognition (Regulatory) Agreement
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
MRFG	Mutual Recognition Facilitation Group (Regulatory)
MRSA	Methicillin Resistant Staphylococcus Aureas
MS	Multiple Sclerosis
MS	Master Schedule
MTS	Medicines Testing Scheme
NAA	National Audit Office
NAMAS	National Accreditation of Measurement and Sampling
NAPPO	North American Plant Protection Organisation
NAFP	National Association of Fundholding Practices
NAPC	National Association for Primary Care
NC	Non-Conformance
NCCL	National Committee for Clinical Laboratory Science
NCs	Notifiable Changes
NCDP	National Clinical Development Plan
NCE	New Chemical Entity
NCR	Non-Conformance Report
NDA	New Drug Application
NDAB	National Drugs Advisory Board (now NMB) (Ireland)
NDSs	New Drug Submissions
NEPG	North East Pharmaceutical Group
NFAP	National Framework for Assessing Performance
NERA	National Economic Research Associates (Part of PPBH)
NGO	Non-Governmental Organisation
NHS	National Health Service

NHS net	National Health Service for Health Care Professionals
NHSC	National Health Service Confederation
NHSE	National Health Service Executive
NHSIS	NHS in Scotland
NICE	National Institute for Clinical Excellence
NIDDM	Non-Insulin Dependent-Diabetes Mellitus
NIBSC	National Institute of Biological Standards and Control
NMB	National Medicines Board
NME	New Molecular Entity
NPA	National Pharmaceutical Association
NPC	National Prescribing Centre (NHSE)
NPCRDC	National Primary Care Research & Development Centre
NPV	Net Present Value
NSAID	Non-Steroidal, Anti Inflammatory Drug
NSF	National Service Framework
NTM	New Transatlantic Market Place
NVQ	National Vocational Qualification
NWPG	North West Pharmaceutical Group
OAT	Out of Area Treatment
OBGYN	Obstetric/Gynaecology
OC	Oral Contraceptives
Od	Once Daily
OECD	Organisation for Economic Co-operation and Development
OHE	Office for Health Economics (part of the ABPI)
OH&S	Occupational Health and Safety
OHSAS	Occupational Health and Safety Assessment Series
ONS	Office of National Statistics
OOS	Out-of-Specification
OPD	Original Pack Dispensing
OQ	Operating Qualification
OTC	Over the Counter
OTS	Opportunities to see (Advertising Criteria)
P	Pharmacy Medicine
PA	Pharmacy Advisor
PA	Patients Association
PA	Product Authorisation (Ireland)
PACT	Prescribing, Analyses and Cost Data
PAI	Pre-Approval Inspection
PBM	Pharmaceutical Benefit Management (US)
PCG	Primary Care Group (England) see also LHC (Scotland), LHG (Wales), PCP (N. Ireland)
PCP	Primary Care Partnership (N Ireland)
PCCP	Primary Care Commissioning Pilot (Scotland)
PCO	Primary Care Organisation
PCT	Primary Care Trust
PCT	Patent Co-operation Treaty
PD	Pharmacodynamics
PDA	Parenteral Drug Association

PES	Public Expenditure Survey
PFI	Private Finance Initiative
PGEA	Post Graduate Education Allowance
PGGP	Primary Care Group Pilot (England)
PharMIG	Pharmaceutical Microbiology Interest Group
PH.EUR	European Pharmacopoeia
PhRMA	Pharmaceutical Research & Manufacturers of America (US equivalent of ABPI)
PI	Parallel Import
PI	Prescribing Information
PI	Principal Investigator
PIC	Pharmaceutical Industry Council
PIC	Pharmaceutical Inspection Convention
PICs	Pharmaceutical Industry Co-operation Scheme
PIL	Patient Information Leaflet
PJ	Pharmaceutical Journal
PK	Pharmacokinetics
PL	Product License
PLA	Product License Application
PLE	Product Line Extension
PMCPA	Prescription Medicines Code of Practice Authority (Part of the ABPI)
PMS	Post Marketing Surveillance
pMDI	Pressurised Metered Dose Inhaler
POM	Prescription Only Medicine
PPA	Prescription Pricing Authority
PPBH	Pharmaceutical Partners for Better Healthcare
PPO	Preferred Provider Organisation
PPRS	Pharmaceutical Price Regulation Scheme
PQ	Performance Qualification
PRODIGY	Prescribing Rationally with Decision support In General practice study
PSBR	Public Sector Borrowing Requirement
PSNC	Pharmaceutical Services Negotiating Committee
PSUR	Periodic Safety Update Report
PVS	Physician Verification Service (US)
QA	Quality Assurance
QAU	Quality Assurance Unit
QALYs	Quality Adjusted Life Years
QC	Quality Control
QM	Quality Management
QMG	Quality Management Group
QMS	Quality Management System
QoL	Quality of Life
QOS	Quality Overall Summary
QP	Qualified Person
QS	Quality System
RCGP	Royal College of General Practitioners
RCOG	Royal College of Obstetricians and Gynaecologists
RCP	Royal College of Physicians

RCS	Royal College of Surgeons
RCT	Randomised Clinical Trials
R&D	Research and Development
RDE	Remote Data Entry
RDS	Research Defence Society
REC	Research Ethics Committee
RGN	Registered General Nurse
RHA	Regional Health Authority
RMS	Reference Member State
RNA	Ribonucleic Acid
RO	Regional Office
ROC	Return on Capital
ROI	Return on Investment
ROS	Return on Sales
RP	Responsible Person
RphO	Regional Pharmaceutical Officer
RPSGB	Royal Pharmaceutical Society of Great Britain
RSC	Royal Society of Chemistry
RSM	Royal Society of Medicine
RTP	Rapid Transfer Port
Rx	Prescription
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAMM	Safety Assessment of Marketed Medicines
SANDs	Supplemental Abbreviated New Drug Submissions
SATs	System Acceptance Tests
SCI	Society of the Chemical Industry
SCF	Scientific Committee on Food
SCMO	Senior Clinical Medical Officer
SCST	Society of Commercial Seed Technologists
SD	Study Director
SDV	Source Data Validation: Source Document Verification
SEPIG	South East Pharmaceutical Industry Group
SEQM	Service European de la Qualite du Medicament
SERM	Selective Oestrogen Receptor Modular
SHA	Strategic Health Authority
SHTAC	Scottish Health Technology Assessment Centre (Equivalent to NICE)
SI	Statutory Instrument
SI Units	Système International d'unités
SIGAR	Special Interest Group on Adverse Reactions
SIMR	Seriously III for Medical Research
SLS	Selected List Scheme
SMO	Site Management Organisation
SmPC/SPC	Summary of Product Characteristics
SNDA	Supplemental New Drug Application
SNDs	Supplemental New Drug Submissions
SNIP	Syndicat National de L'Industrie Pharmaceutique (French equivalent to ABPI)
SOP	Standard Operating Procedure

SP	Study Plan
SPC	See SmPC above
SPC	Supplementary Protection Certificate (Extra Patent Life)
SPG	Scottish Pharmaceutical Group
STOA	Scientific and Technical Options Analysis Group (EU)
SWOT	Strengths, Weaknesses, Opportunities, Threats
SSRI	Selective Serotonin Reuptake Inhibitor
TABD	Trans Atlantic Business Dialogue
Tid	Three times Daily
TIGR	The Institute for Genomic Research
TPA	Tissue Plasminogen Activator (clot buster)
TRIPs	Agreement on Trade Related aspects of Intellectual Property Rights
TSCA	The Toxic Substances Control Act (USA)
TVC	Total Viable Count
UDV	Unit Dose Vial
UGL	Usage Guide Line
UKAS	United Kingdom Accreditation Service
UKECA	United Kingdom Ethics Committee Authority
UKNEQAS	United Kingdom External Quality Assessment Service
UKPTO	United Kingdom Patent and Trade Mark office
UNDP	United Nations Development Programme
UNEP	United Nations Environment Programme
UNECE	UN Economic Commission for Europe
UNIDO	United Nations Industrial Development Organisation
UPOV	International Union for the Protection of New Varieties of Plants
URL	Universal Resource Locator (internet)
URS	User Requirement Specification
USP	Unique Selling Proposition
USP	United States Pharmacopoeia
USPTO	United States Patent and Trade Mark Office
VFA	Verband Forschender Arzneimittelhersteller (German research based Companies' industry association)
VHO	Voluntary Health Organisation
VMP	Validation Master Plan
WAN	Wide Area Network
WBCSD	World Business Council for Sustainable Development
WDL	Wholesalers Dealers License
WHA	World Health Assembly
WHO	World Health Organisation
WIPO	World Intellectual Property Organisation
WTO	World Trade Organisation

More abbreviations and acronyms can be found at <http://www.pharma-lexicon.com>

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# Appendix GLP Comparison, OECD, USA and Japan







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Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
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
## 1. General Provisions







General Provisions – Scope	Sec. I. 1	Sec. 58.1 (a)  Sec. 58.1 (b)	Sec. 160.1 (a)  Sec. 160.1 (b)	Sec. 792.1 (a)  Sec. 792.1 (b)  Sec. 792.1 (c)	Article 1  *1 *1(1)  *1(2)  *2	Article 1
General Provisions Studies Conducted Under Contracts		Sec. 58.10	Sec. 160.10	Sec. 792.10	Article 4  4.1 4.2 4.3 *3(2) Article 4	Article 3
General Provisions – Authority Inspection		Sec. 58.15 (a)	Sec. 160.15 (a)	Sec. 792.15 (a)		
General Provisions – Consequences of Refusing to Permit Inspection		Sec. 58.15 (b)	Sec. 160.15 (b)	Sec. 792.15 (b)  Sec. 792.15 (c)		
General Provisions – Statement of Compliance or Non-Compliance			Sec. 160.12	Sec. 792.12		
General Provisions – Effects of Non-Compliance			Sec. 160.17 (a)  Sec. 160.17 (b)	Sec. 792.17 (a)  Sec. 792.17 (b)		

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
				Sec. 792.17 (c)		

## 2. Definitions

Good Laboratory Practice (GLP)	Sec. I 2.1.1					
Act		Sec. 58.3 (a)				
EPA			Sec. 160.3	Sec. 792.3		
FDA			Sec. 160.3	Sec. 792.3		
FFDCA			Sec. 160.3			
FIFRA			Sec. 160.3			
TSCA				Sec. 792.3		
Testing Facility	Sec. I 2.2.1	Sec. 58.3 (g)	Sec. 160.3	Sec. 792.3		Article 2 (2)
Test Site	Sec. I 2.2.2					
Test Facility Management	Sec. I 2.2.3					Article 2 (3)

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>Test Site Management</b>	Sec. I 2.2.4					
<b>Sponsor</b>	Sec. I 2.2.5	Sec. 58.3 (f)	Sec. 160.3	Sec. 792.3		Article 2 (1)
<b>Study Director</b>	Sec. I 2.2.6	Sec. 58.3 (m)	Sec. 160.3	Sec. 792.3		Article 2 (4)
<b>Principal Investigator</b>	Sec. I 2.2.7					
<b>Person</b>		Sec. 58.3 (h)	Sec. 160.3	Sec. 792.3		
<b>Quality Assurance</b>	Sec. I 2.2.8	Sec. 58.3 (l)	Sec. 160.3	Sec. 792.3		Article 2 (5)
<b>Standard Operating Procedures</b>	Sec. I 2.2.9					Article 2 (12)
<b>Master Schedule</b>	Sec. I 2.2.10					Article 2 (10)
<b>Non-clinical Laboratory Study</b>	Sec. I 2.3.1	Sec. 58.3 (d)	Sec. 160.3	Sec. 792.3		Article 2 (7)
<b>Short-Term Study</b>	Sec. I 2.3.2					
<b>Study</b>	Sec. I 2.3.3					Article 2 (11)
<b>Study Plan Amendment</b>	Sec. I 2.3.4					

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>Study Plan Deviation</b>	Sec. I 2.3.5					
<b>Final Report</b>						Article 2 (15)
<b>Test System</b>	Sec. I 2.3.6	Sec. 58.3 (i)	Sec. 160.3	Sec. 792.3	Article 2 (3)	Article 2 (8)
<b>Raw Data</b>	Sec. I 2.3.7	Sec. 58.3 (k)	Sec. 160.3	Sec. 792.3	Article 2 (5) *3(1) Article 2	Article 2 (13)
<b>Record Document</b>						Article 2 (14)
<b>Specimen</b>	Sec. I 2.3.8	Sec. 58.3 (j)	Sec. 160.3	Sec. 792.3	Article 2 (4)	
<b>Experimental Starting Date</b>	Sec. I 2.3.9		Sec. 160.3	Sec. 792.3		
<b>Experimental Completion Date</b>	Sec. I 2.3.10		Sec. 160.3	Sec. 792.3		
<b>Study Initiation Date</b>	Sec. I 2.3.11	Sec. 58.3 (o)	Sec. 160.3	Sec. 792.3		
<b>Study Completion Date</b>	Sec. I 2.3.12	Sec. 58.3 (p)	Sec. 160.3	Sec. 792.3		
<b>Archive</b>						Article 2 (6)







Requirements	OECD	FDA	FIFRA	TSCA	MHW	MAFF
<b>Test Item</b>	Sec. I 2.4.1	Sec. 58.3 (b)	Sec. 160.3	Sec. 792.3	Article 2 (1)	
<b>Reference/Control Item</b>	Sec. I 2.4.2	Sec. 58.3 (c)	Sec. 160.3 Sec. 160.3	Sec. 792.3 Sec. 792.3	Article 2 (2)	
<b>Batch</b>	Sec. I 2.4.3	Sec. 58.3 (n)	Sec. 160.3	Sec. 792.3		Article 2 (9)
<b>Vehicle</b>	Sec. I 2.4.4		Sec. 160.3	Sec. 792.3		
<b>Carrier</b>			Sec. 160.3	Sec. 792.3		
<b>Application for Research or Marketing Permit</b>		Sec. 58.3 (e)	Sec. 160.3			
<b>3. Organization and Personnel (O&amp;P)</b>						
<b>O&amp;P – Testing Facility Management (TFM) – Assure Compliance with GLP</b>	Sec. II 1.1.1					
<b>O&amp;P – TFM – Responsibilities</b>	Sec. II 1.1.2.a				Article 6	Article 5.1
<b>O&amp;P – TFM – Designate a Study Director</b>	Sec. II 1.1.2.g	Sec. 58.31 (a)	Sec. 160.31 (a)	Sec. 729.31 (a)	Article 6.(1)	Article 5.2(2)
<b>O&amp;P – TFM – Replace a Study Director</b>	Sec. II 1.1.2.g	Sec. 58.31 (b)	Sec. 160.31 (b)	Sec. 792.31.(b)	*3(4) Article 6	

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	MAFF ✱
O&P – TFM – Establish a Quality Assurance Unite (QAU)	Sec. II 1.1.2.f	Sec. 58.31 (c)	Sec. 160.31 c	Sec. 792.31.c	Article 6.(2) Article 6.(3)	Article 5.2(3)
O&P – TFM – Assure Availability of Resources	Sec. II 1.1.2.n	Sec. 58.31 (e)	Sec. 160.31 (e)	Sec. 792.31 (e)	Article 6.(6) Article 6.(9)	Article 5.2(1) Article 5.2(10)
O&P – TFM – Assure Personnel Understand their Functions	Sec. II 1.1.2.d	Sec. 58.31 (f)	Sec. 160.31 (f)	Sec. 792.31 (f)		
O&P – TFM – Assure Appropriate SOPs	Sec. II 1.1.2.e				Article 6.(5)	Article 5.2.(7)
O&P – TFM – Assure Corrective Actions		Sec. 58.31 (g)	Sec. 160.31 (g)	Sec. 792.31 (g)		Article 5.2.(8)
O&P – TFM – Assure Principal Investigator (PI)	Sec. II 1.1.2.h					
O&P – TFM – Assure Study Director Approves Protocol	Sec. II 1.1.2.i					Article 5.2(6)
O&P – TFM – Assure Protocol to QA	Sec. II 1.1.2.j					
O&P – TFM – Assure Historical SOPs	Sec. II 1.1.2.k					
O&P – TFM – Assure Archivist	Sec. II 1.1.2.l					Article 5.2(4)







Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	MAFF ✱
<b>O&amp;P – TFM – Assure Master Schedule</b>	Sec. II 1.1.2.m					Article 5.2(5)
<b>O&amp;P – TFM – Clear Communication</b>	Sec. II 1.1.2.o					
<b>O&amp;P – TFM – Assure Appropriate Test and Reference Items</b>	Sec. II 1.1.2.p	Sec. 58.31 (d)	Sec. 160.31 (d)	Sec. 792.31 (d)	Article 6.(4)	Article 5.2(9)
<b>O&amp;P – TFM – Validation of Computerized Systems</b>	Sec. II 1.1.2.q					
<b>O&amp;P – TFM – Test Site Management Responsibilities</b>	Sec. II 1.1.3					
<b>O&amp;P – Study Director – Responsibilities</b>	Sec. II 1.2.1	Sec. 58.33	Sec. 160.33	Sec. 792.33		
<b>O&amp;P – Study Director – Protocol Approval</b>	Sec. II 1.2.2.a	Sec. 58.33 (a)	Sec. 160.33 (a)	Sec. 792.33 (a)	Article 7(1)	Article 6(1)
<b>O&amp;P – Study Director – Assure QAU has Protocol</b>	Sec. II 1.2.2.b					
<b>O&amp;P – Study Director – Assure Personnel Have Protocol and SOPs</b>	Sec. II 1.2.2.c					
<b>O&amp;P – Study Director – Assure Principle Investigator Role</b>	Sec. II 1.2.2.d					
<b>O&amp;P – Study Director – Recording and Verification of Data</b>	Sec. II 1.2.2.f	Sec. 58.33 (b)	Sec. 160.33 (b)	Sec. 792.33 (b)	Article 7(2)	Article 6(2)



Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	MAFF ✱
O&P – Study Director – Unforeseen Circumstances	Sec. II 1.2.2.e	Sec. 58.33 (c)	Sec. 160.33 (c)	Sec. 792.33 (c)	Article 7(3)	Article 6(3) Article 6(4) Article 6(5)
O&P – Study Director – Test System		Sec. 58.33 (d)	Sec. 160.33 (d)	Sec. 792.33 (d)	Article 7(5)	
O&P – Study Director – GLP Compliance	Sec. II 1.2.2.h	Sec. 58.33 (e)	Sec. 160.33 (e)	Sec. 792.33 (e)	Article 7(4)	
O&P – Study Director – Validation of Computerized Systems	Sec. II 1.2.2.g					
O&P – Study Director – Other Duties					Article 7(7)	Article 6(6)
O&P – Study Director – Archiving	Sec. II 1.2.2.i	Sec. 58.33 (f)	Sec. 160.33 (f)	Sec. 792.33 (f)	Article 7(6)	Article 6(7)
O&P – Principal Investigator – Responsibilities	Sec. II 1.3					
O&P – Personnel – Responsibilities	Sec. II 1.4.2					
O&P – Personnel – Recording Data	Sec. II 1.4.3					
O&P – Personnel – Training and Experience	Sec. II 1.4.1	Sec. 58.29 (a)	Sec. 160.29 (a)	Sec. 792.29 (a)	Article 5 Article 6.(7)	Article 4.1

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>O&amp;P – Personnel – Maintenance of Training Records and Job Descriptions</b>	Sec. II 1.1.2.c	Sec. 58.29 (b)	Sec. 160.29 (b)	Sec. 792.29 (c)	Article 6.(8)	Article 5.2(1)
<b>O&amp;P – Personnel – Availability of Personnel</b>	Sec. II 1.1.2.b	Sec. 58.29 (c)	Sec. 160.29 (c)	Sec. 792.29 (c)		
<b>O&amp;P – Personnel – Health Precautions</b>	Sec. II 1.4.4	Sec. 58.29 (d)	Sec. 160.29 (d)	Sec. 792.29 (d)	Article 5.2	Article 4.2(1)
<b>O&amp;P – Personnel – Clothing</b>	S	Sec. 58.29 (e)	Sec. 160.29 (e)	Sec. 792.29 (e)	*3(3) Article 5	
<b>O&amp;P – Personnel – Illness Precautions</b>	Sec. 1.4.4	Sec. 58.29 (f)	Sec. 160.29 (f)	Sec. 792.29 (f)	*3(3) Article 5	Article 4.2.(2)
<b>O&amp;P – QAU – Responsibilities</b>	Sec. II 2.1.1  Sec. II 2.1.2	Sec. 58.35 (a)	Sec. 160.35 (a)	Sec. 792.35 (a)	Article 8 Article 8(10)	Article 7.1  Article 8.3
<b>O&amp;P – QAU – Independence</b>	Sec. II 2.1.3	Sec. 58.35 (a)	Sec. 160.35 (a)	Sec. 792.35 (a)	Article 8.2	
<b>O&amp;P – QAU – Maintenance of Master Schedule Copies</b>	Sec. II 2.2.1 (a)	Sec. 58.35 (b) (1)	Sec. 160.35 (b) (1)	Sec. 792.35 (b) (1)	Article 8(1)	Article 7.2(1)
<b>O&amp;P – QAU – Maintenance of Copies of Protocols</b>	Sec. II 2.2.1 (a)	Sec. 58.35 (b) (2)	Sec. 160.35 (b) (2)	Sec. 792.3 (b) (2)	Article 8(2)	Article 7.2(2)

Requirements	OECD	FDA	FIFRA	TSCA	MHW	MAFF
<b>O&amp;P – QAU – Verification of Content of Protocol</b>	Sec. II 2.2.1 (b)					
<b>O&amp;P – QAU – Inspections</b>	Sec. II 2.2.1.c	Sec. 58.35 (b) (3)	Sec. 160.35 (b) (3)	Sec. 792.35 (b) (3)	Article 8(3)	Article 7.2.(3)
<b>O&amp;P – QAU – Review of Final Report</b>	Sec. II 2.2.1.d	Sec. 58.35 (b) (6)	Sec. 160.35 (b) (6)	Sec. 792.35 (b) (6)	Article 8(7)	Article 7.2.(7)
<b>O&amp;P – QAU – Reporting</b>	Sec. II 2.2.1.e	Sec. 58.35 (b) (3) Sec. 58.35 (b) (4)	Sec. 160.35 (b) (3) Sec. 160.35 (b) (4)	Sec. 792.35 (b) (3) Sec. 792.35 (b) (4)	Article 8(4)  Article 8(5)	Article 7.2.(4)  Article 7.2.(5)
<b>O&amp;P – QAU – Assurance Deviations are Authorized</b>		Sec. 58.35 (b) (5)	Sec. 160.35 (b) (5)	Sec. 792.35 (b) (5)	Article 8(6)	Article 7.2.(6)
<b>O&amp;P – QAU – Final Report Statement</b>	Sec. II 2.2.1.f	Sec. 58.35 (b) (7)	Sec. 160.35 (b) (7)	Sec. 792.35 (b) (5)	Article 8(8)	
<b>O&amp;P – QAU – Responsibilities and Procedures</b>		Sec. 58.35 (c)	Sec. 160.35 (c)	Sec. 792.35 (c)	Article 8(9)	Article 7.2.(8) Article 7.3
<b>O&amp;P – QAU – Contact with Representatives of Authority</b>		Sec. 58.35 (d)	Sec. 160.35 (d)	Sec. 792.35 (d)		
<b>4. Facilities</b>						
<b>Facilities – General Requirements</b>	Sec. II 3.1.1	Sec. 58.41	Sec. 160.41	Sec. 792.41	Article 9	Article 8

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
	Sec. II 3.1.2					
<b>Facilities – Animal Care Facilities – Animal Rooms</b>	Sec. II 3.2.1	Sec. 58.43 (a)	Sec. 160.43 (a) Sec. 160.43 (a) (1) Sec. 160.43 (a) (2)	Sec. 792.43 (a) Sec. 792.43 (a) (1) Sec. 792.43 (a) (2)	Article 9.2 *3(5) Article 9 a.	Article 9.2
<b>Facilities – Animal Care Facilities – Disease Control Areas</b>	Sec. II 3.2.2	Sec. 58.43 (c)	Sec. 160.43 (c)	Sec. 792.43 (c)	*3(5) Article 9 c,(b)	Article 9.4
<b>Facilities – Animal Care Facilities – Isolation of Biohazardous Agents</b>	Sec. II 3.2.1	Sec. 58.43 (b)	Sec. 160.43 (b)	Sec. 792.43 (b)	*3(5) Article 9 c,(a) *3(5) Article 9 f,(a)	Article 9.3
<b>Facilities – Animal Care Facilities – Environmental Control</b>			Sec. 160.43 (e)	Sec. 792.43 (e)		Article 9.1
<b>Facilities – Animal Care Facilities – Marine Test Organisms</b>			Sec. 160.43 (f)	Sec. 792.43 (f)		
<b>Facilities – Animal Care Facilities – Freshwater Test Organisms</b>			Sec. 160.43 (g)	Sec. 792.43 (g)		
<b>Facilities – Animal Care Facilities – Plants</b>			Sec. 160.43 (h)	Sec. 792.43 (h)		

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	MAFF ✱
<b>Facilities – Animal Care Facilities – Animal Supply Storage</b>	Sec. II 3.2.3	Sec. 58.45	Sec. 160.45 (a) Sec. 160.45 (b) Sec. 160.45 (c)	Sec. 792.45 (a) Sec. 792.45 (b) Sec. 792.45 (c)	*3(5) Article 9 b.	Article 10
<b>Facilities – Test and Reference Items – Preventing Contamination</b>	Sec. II 3.3.1	Sec. 58.47 (a)	Sec. 160.47 (a)	Sec. 792.47 (a)	Article 9.3 *3(5) Article 9 d.	Article 11.1
<b>Facilities – Test and Reference Items – Storage areas</b>	Sec. II 3.3.2	Sec. 58.47 (b)	Sec. 160.47 (b)	Sec. 792.47 (b)		Article 11.2
<b>Facilities – Archiving</b>	Sec. II 3.4	Sec. 58.51	Sec. 160.51	Sec. 792.51	Article 9.4	Article 13
<b>Facilities – Waste Disposal</b>	Sec. II 3.5	Sec. 58.43 (d)	Sec. 160.43 (d)	Sec. 792.43 (d)	*3(5) Article 9 c, (c)	Article 9.5
<b>Facilities – Laboratory Operation Areas</b>		Sec. 58.49	Sec. 160.49	Sec. 792.49	*3(5) Article 9 e *3 (5) Article 9 f. (b)	Article 12
<b>Facilities – Offices and Accommodations</b>						Article 14.1 Article 14.2

## 5. Equipment, Material and Reagent







Requirements	OECD	FDA	FIFRA	TSCA	MHW	MAFF
<b>Equipment - Design</b>	Sec. II 4.1 Sec. II 4.3	Sec. 58.51	Sec. 160.61	Sec. 792.61	Article 10	Article 15 Article 16
<b>Equipment – Maintenance and Calibration</b>	Sec. II 4.2	Sec. 58.63 (a)	Sec. 160.63 (a)	Sec. 792.63 (a)	Article 10.2 *3(6) Article 10	Article 17 Article 17.1
<b>Equipment – Standard Operating Procedures (SOPs)</b>		Sec. 58.63 (b)	Sec. 160.63 (b)	Sec. 792.63 (b)		Article 17.2
<b>Equipment – Written Records</b>		Sec. 58.63 (b)	Sec. 160.63 (b)	Sec. 792.63 (b)	Article 10.3	Article 17.3
<b>Materials, Reagents – Labelling</b>	Sec. II 4.4	Sec. 58.83	Sec. 160.83	Sec. 792.83	Article 14	Article 19.1 Article 19.2

## 6. Test System







<b>Test System – Physical/Chemical</b>	Sec. II 5.1.1 5.1.2		Sec. 160.135 (a) Sec. 160.135 (b)	Sec. 792.135 (a) Sec. 792.135 (b)		
<b>Test System – SOPs</b>		Sec. 58.90 (a)	Sec. 160.90 (a)	Sec. 792.90 (a)		
<b>Test System – Isolation of Newly Received Test System</b>	Sec. II 5.2.2	Sec. 58.90 (b)	Sec. 160.90 (b)	Sec. 792.90 (b)	Article 12	Article 20.1

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	* MAFF
<b>Test System – Disease</b>	Sec. II 5.2.2	Sec. 58.90 (c)	Sec. 160.90 (c)	Sec. 792.90 (c)	Sec. Article 12.2 *3(8) Article 12 a	Article 20.2 Article 20.3 Article 20.4
<b>Test System – Receipt</b>	Sec. II 5.2.3					
<b>Test System – Acclimatization</b>	Sec. II 5.2.4		Sec. 160.90 (j)	Sec. 792.90 (j)	Article 12.3	Article 20.5
<b>Test System – Identification</b>	Sec. II 5.2.5	Sec. 58.90 (d)	Sec. 160.90 (d)	Sec. 792.90 (d)	Article 12.4 *3(8) Article 12b(a)	Article 20.6 Article 20.7
<b>Test System – Housing</b>	Sec. II 5.2.1 Sec. II 5.2.7	Sec. 58.90 (e)	Sec. 160.90 (e) Sec. 160.90 (e) I	Sec. 792.90 (e) Sec. 792.90 (e) I	*3(8) Article 12 b	Article 20.8 Article 20.9
<b>Test System – Cleaning, Sanitization</b>	Sec. II 5.2.6	Sec. 58.90 (f)	Sec. 160.90 (f)	Sec. 792.90 (f)	*3(8) Article 12c (a)	Article 20.10
<b>Test System – Feed and Water</b>	Sec. II 5.2.6	Sec. 58.90 (g)	Sec. 160.90 (g)	Sec. 792.90 (g)	Article 12.5 *3(8) Article 12c (c)	Article 20.12









Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>Test System – Bedding</b>	Sec. II 5.2.6	Sec. 58.90 (h)	Sec. 160.90 (h)	Sec. 792.90 (h)	*3(8) Article 12c (b)	Article 20.11
<b>Test System – Pest Control</b>	Sec. II 5.2.6	Sec. 58.90 (i)	Sec. 160.90 (i)	Sec. 792.90 (i)	*3(8) Article 12c (d) (e)	Article 20.13
<b><u>7. Test and Reference Items</u></b>						
<b>Test and Reference Items - Handling</b>	Sec. II 6.1.1 Sec. II 6.1.2	Sec. 58.107	Sec. 160.107	Sec. 792.107	Article 13.3  *3(9) Article 13 a (a–c)	Article 22
<b>Test and Reference Items - Labelling</b>	Sec. II 6.1.3	Sec. 58.105 (c)	Sec. 160.105 (c)	Sec. 792.105 (c)	*3(9) Article 13 a (f)	Article 21.4
<b>Test and Reference Items – Characterization</b>	Sec. II 6.2.1 Sec. II 6.2.2 Sec. II 6.2.3	Sec. 58.105 (a)	Sec. 160.105 (a)	Sec. 792.105 (a)	Article 13  *3(9) Article 13 a (d)	Article 21.1 Article 21.2
<b>Test and Reference Items – Stability</b>	Sec. II 6.2.4	Sec. 58.105 (b)	Sec. 160.105 (b)  Sec. 160.105 (e)	Sec. 792.105 (b)  Sec. 792.105 (e)	*3(9) Article 13a (e)	Article 21.3

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ?	MHW ☐	* MAFF
<b>Test and Reference Items – Reserving Samples</b>	Sec. II 6.2.6	Sec. 58.105 (d)	Sec. 160.105 (d)	Sec. 792.105 (d)		Article 21.5
<b>Test and Reference Items – Uniformity Concentration and Stability of Mixtures</b>	Sec. II 6.2.5	Sec. 58.113 (a) (1) 58.113 (a) (2)	Sec. 160.113 (a)	Sec. 792.113 (a)	Article 13.2  *3(9) Article 13 b (b)	Article 23.1
<b>Test and Reference Items – Expiration Date of Mixtures</b>		Sec. II 58.113 (c)	Sec. 160.113 (b)	Sec. 792.90 (b)	*3(8) Article 13 b (b)	Article 23.2
<b>Test and Reference Items – Interference of Vehicle</b>			Sec. 160.113 (c)	Sec. 792.113 (c)		
<b>8. Standard Operating Procedures (SOPs)</b>						
<b>Standard Operating Procedures (SOPs)</b>	Sec. II 7.1	Sec. 58.81 (a)	Sec. 160.81 (a)	Sec. 792.81 (a)	*3(7) Article 11 a	
<b>SOPs - Deviations</b>	Sec. II 7.3	Sec. 58.81 (a)	Sec. 160.81 (a)	Sec. 792.81 (a)	Article 11.4 Article 11.5	
<b>SOPs – Significant Changes</b>		Sec. 58.81 (a)	Sec. 160.81 (a)	Sec. 792.81 (a)	Article 11.3	Article 18.2 Article 18.3
<b>SOPs - Revisions</b>	Sec. II 7.1					

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>SOPs - Availability</b>	Sec. II 7.2	Sec. 58.81 (c)	Sec. 160.81 (c)	Sec. 792.81 (c)	Article 11.2 *3(7) Article 11 b	
<b>SOPs – Historical File</b>	Sec. II 10.1 (f)	Sec. II 58.81 (d)	Sec. 160.81 (d)	Sec. 792.81 (d)		Article 18.3
<b>SOPs – Contents</b>  <i>Test and reference Items:</i> <i>Apparatus</i> <i>Computerized Systems</i> <i>Materials, Reagents and Solutions</i> <i>Records Keeping, Reporting, Storage and Retrieval</i> <i>Test system</i> <i>Quality Assurance Procedures</i>  <i>Other</i>	7.4 7.4.1 7.4.2 7.4.3 7.4.4 7.4.5	Sec. 58.81 (b)	160.81 (b)	792.81 (b)	Article 11.(1–14) *3(7) Article 11c, d	Article 18.1
<b>9. Performance of the study</b>						
<b>Performance of the Study – Written Protocol</b>	Sec. II 8.1.1	Sec. 58.120 (a)	Sec. 160.120 (a)	Sec. 792.120 (a)	Article 15 *3(10) Article 15 a	Article 24
<b>Performance of the Study – Protocol Amendment</b>	Sec. II 8.1.2. (a)	Sec. 58.120 (b)	Sec. 160.120 (b)	Sec. 792.120 (b)	Article 15.2	Article 24.2

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	MAFF ✱
<b>Performance of the Study – Protocol Deviation</b>	Sec. II 8.1.2 (b)					
<b>Performance of the Study – Short-Term Studies</b>	Sec. II 8.1.3					
<b>Performance of the Study – Protocol Content</b>	Sec. II 8.2.1 Sec. II 8.2.2 Sec. II 8.2.3 8.2.3a 8.2.3b Sec. II 8.2.4 Sec. II 8.2.5 Sec. II 8.2.6	Sec. 58.120 (a)	Sec. 160.120 (a)	Sec. 792.120 (a)	Article 15 *3(10) Article 15b (a–c)	Article 24
<i>Identification of the Study, the Test Item and Reference Item Information Concerning the Sponsor and the Test Facility</i>						
<i>Dates</i>						
<i>The Methods Issues</i>						
<i>Records</i>						
<i>Other</i>						
<b>Performance of the Study – Identification of Specimens</b>	Sec. II 8.3.1	Sec. 58.130 (c)	Sec. 160.130 (c)	Sec. 792.130 (c)	*3(11) Article 16a. (a–b)	Article 25.2 Article 25.3
<b>Performance of the Study – Conduct</b>	Sec. II 8.3.2	Sec. 58.130 (a)	Sec. 160.130 (a)	Sec. 792.130 (a)	Article 16 Article 3	Article 25.1

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>Performance of the Study – Test System</b>		Sec. 58.130 (b)	Sec. 160.130 (b)	Sec. 792.130 (a)		
<b>Performance of the Study – Record of Gross Findings and Pathologist</b>		Sec. 58.130 (d)	Sec. 160.130 (d)	Sec. 792.130 (d)	*3(11) Article 16 a (c)	Article 25.4
<b>Performance of the Study – Manual Recording</b>	Sec. II 8.3.3	Sec. 58.130 (e)	Sec. 160.130 (e)	Sec. 792.130 (e)	Article 16.2  *3(11) Article 16b(a)	Article 25.5 (1–2)
<b>Performance of the Study – Changes of the Manual Recording</b>	Sec. II 8.3.4	Sec. 58.130 (e)	Sec. 160.130 (e)	Sec. 792.130 (e)	Article 16.3  *3(11) Article 16c(c)	Article 25.5 (3)
<b>Performance of the Study – Automated Recording Data</b>	Sec. II 8.3.5	Sec. 58.130 (e)	Sec. 160.130 (e)	Sec. 792.130 (e)	*3(11) Article 16b (b)	Article 25.5 (2)
<b>Performance of the Study – Changes of the Automated Recording Data</b>	Sec. II 8.3.5	Sec. 58.130 (e)	Sec. 160.130 (e)	Sec. 792.130 (e)	*3(11) Article 16c (c)	Article 25.5 (3)
<b>Performance of the Study – Unexpected Things</b>					Article 16.4	Article 25.6

## 10. Final Report

Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☯	MHW ☐	* MAFF
<b>Final Report</b>	Sec. II 9.1.1	Sec. 58.185 (a)	Sec. 160.185 (a)	Sec. 792.185 (a)		
<b>Final Report – Signing</b>	Sec. II 9.1.2  Sec. II 9.1.3	Sec. 58.185 (b)	Sec. 160.185 (b)	Sec. 792.185 (b)	*3(12) Article 17 a	
<b>Final Report – Correction and Addition</b>	Sec. II 9.1.4	Sec. 58.185 (c)	Sec. 160.185 (c)	Sec. 792.185 (c)	Article 17.2	Article 26.3
<b>Final Report – Reformatting</b>	Sec. II 9.1.5					
<b>Final Report – Copy</b>			Sec. 160.185 (d)	Sec. 792.185 (d)		
<b>Final Report – Content</b> <i>Identification of the Study, the Test Item and Reference Item Information Concerning the Sponsor and the Test Facility</i>  <i>Dates:</i>	Sec. II 9.2 9.2.1 Sec. II 9.2.2 Sec. II 9.2.3					
<i>Statement:</i>  <i>Description of Materials and Test Methods</i>  <i>Results</i>  <i>Storage</i>  <i>Other</i>	Sec. II 9.2.4 Sec. II 9.2.5 Sec. II 9.2.6 Sec. II 9.2.7	Sec. 58.185 (a)	160.185 (a)	792.185 (a)	Article 17	Article 26.1







Requirements	OECD ✂	FDA ➤	FIFRA ●	TSCA ☼	MHW ☐	MAFF ✱
					*3(12) Article 17b (a–d)	Article 26.2
<b>11. Archiving</b>						
Archiving – Storage and Retention of Records	Sec. II 10.1	Sec. 58.190 (a)	Sec. 160.190 (a)	Sec. 792.190 (a)	Article 18 *3(13) Article 18 a (a)	Article 27.1
Archiving – Secure Storage	Sec. II 3.4	Sec. 58.190 (b)	Sec. 160.190 (b)	Sec. 792.190 (b)		Article 27.3
Archiving – Indexing	Sec. II 10.2	Sec. 58.190 (e)	Sec. 160.190 (e)	Sec. 792.190 (e)	*3(13) Article 18 a (b)	Article 27.4
Archiving – Archivist and Entering to the Archiving	Sec. II 10.3	Sec. 58.190 (c–d)	Sec. 160.190 (c– d)	Sec. 792.190 (c– d)	Article 18.2 18.3	Article 27.2
Archiving – Facility Goes out of Business	Sec. II 10.4	Sec. 58.195 (h)	Sec. 160.190 (g)	Sec. 792.195 (g)	Article 18.4 Article 18.5	Article 28.4
Archiving – Retentions of Records	Sec. II 10.1	Sec. 58.195 (a) Sec. 58.195 (b)	Sec. 160.195 (a) Sec. 160.195 (b)	Sec. 792.195 (a) Sec. 792.195 (b)		Article 28.3



Requirements	OECD	FDA	FIFRA	TSCA	MHW	MAFF
Archiving – Wet Specimens		Sec. 58.195 (c)	Sec. 160.195 (c)	Sec. 792.195 (c)	*3(13) Article 18b	Article 28.1 Article 28.2
Archiving – Retention of Different Documents		Sec. 58.195 (d)	Sec. 160.195 (d)	Sec. 792.195 (d)	*3(13) Article 18b	
Archiving – Retention of Training Records and Job Descriptions		Sec. 58.195 (e)	Sec. 160.195 (e)	Sec. 792.195 (e)		
Archiving – Retention of Maintenance and Calibration Records		Sec. 58.195 (f)	Sec. 160.195 (f)	Sec. 792.195 (f)		
Archiving – Retention of True Copies		Sec. 58.195 (g)	Sec. 160.195 (i)	Sec. 792.195 (i)		
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## **12. Disqualification of Testing Facility**

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Disqualification of Testing Facility – Grounds for Disqualification		Sec. 58.202 (a–c)				
Disqualification of Testing Facility – Notice of and Opportunity for Hearing on Proposed Disqualification		Sec. 58.204 (a–b)				

Requirements	 OECD	 FDA	 FIFRA	 TSCA	 MHW	 MAFF
<b>Disqualification of Testing Facility – Final Order on Disqualification</b>		Sec. 58.206 (a–b)				
<b>Disqualification of Testing Facility – Actions upon Disqualification</b>		Sec. 58.210 (a–b)				
<b>Disqualification of Testing Facility – Public Disclosure of Information Regarding Disqualification</b>		Sec. 58.213 (a–b)				
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<b>Disqualification of Testing Facility – Suspension or Termination of a Testing Facility by a Sponsor</b>		Sec. 58.217				
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